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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-109 (17-970/S-050)

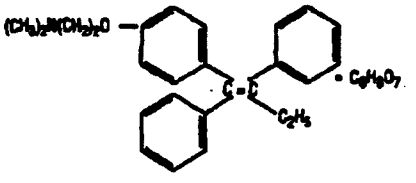
Pharmacology Review(s)

1-11-02

ZD6157 (TAMOXIFEN CITRATE, NOLVADEX™) SUPPLEMENTAL NEW DRUG APPLICATION PEDIATRIC EXCLUSIVITY *PHARMACOLOGY/TOXICOLOGY COVER SHEET*

NDA number: N21-109
Serial number/date/type of submission: SN000/ February 28, 2002
Information to sponsor: Yes (x) No ()
Sponsor: AstraZeneca UK limited, Alderley park, Macclesfield, UK. US agent: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19803
Manufacturer for drug substance: AstraZeneca, UK
Key words: McCune-Albright Syndrome, tamoxifen citrate, precocious puberty in girls
Reviewer name: Wafa Harrouk, Ph.D.
Division name: Division of Endocrine & Metabolic Drug Products
HFD #: 510
Review completion date: 06/27/02
Review #: 1

Drug
Trade name: Nolvadex
Generic Name: Tamoxifen citrate
Code name: ZD6157
Structure:



Chemical name: (Z)-2(4-(1,2-diphenyl-1-butenyl)phenoxyl)-N,N-dimethylethanamine 2-hydroxy-1,2,3-propane tricarboxylate (1:1)
Molecular Formula: $C_{32}H_{37}NO_8$
Molecular Weight: 563.62
Solubility: Soluble in H_2O and in 0.02 N HCl
Relevant INDs/NDAs/DMFs: IND [redacted] IND [redacted] NDA 17-970
Drug class: Hormone receptor modulator
Indication: A type 6 NDA to slow the progression of puberty in girls with gonadotropin-independent precocious puberty due to McCune-Albright Syndrome (MAS)
Clinical formulation: Same as approved tablets.
Route of administration: Oral
Proposed use: Daily dose of 20 mg
Previous pediatric experience: "A one year, open-label, multicenter study to assess the safety, efficacy and pharmacokinetics in pediatric subjects with MAS". Girls (n=28) of ≤10 years of age with classical or atypical MAS and progressive, precocious puberty manifested by signs of pubertal development, menses, and significantly advanced bone age (>2 SD above the mean) were enrolled to receive up to 30 mg/day, single or divided doses of marketed tamoxifen citrate tablets. The majority of enrolled subjects showed a decrease in vaginal bleeding, bone age and height at interim (6 months after the start of treatment). However, most subjects showed episodic asymmetric fluctuations in ovarian size illustrated by the periodic elevations in serum estradiol and estrone throughout the

trial. Furthermore, the mean uterine volume showed a dramatic increase during the study, albeit with a large range of variability (range from 8.5+/- 6.3 cc pretrial to 21.1+/- 11.9 cc at the end of trial). Most adverse events reported were related to pediatric diseases except for 2 serious events involving hospitalization due to one case of asthma exacerbation and one case of bone fracture related to MAS. One patient had elevated AST and ALT enzymes at 6 and 12 months visits and a fourth had alopecia on day 312 of the study. No data was provided for the LH, FSH or plasma estrogen for the pediatric subjects.
The optimal duration of therapy for NOLVADEX has not been determined.

Scientific rationale and background: MAS is a rare disorder characterized by the triad of sexual precocity, fibrous dysplasia and skin pigmentation (café-au-lait spots) commonly seen in female pediatric patients. Endocrine abnormalities include overactive thyroid, adrenal and pituitary glands, and hypophosphatemia. These changes seem to be caused by an activating mutation in the Gsα subunit of G protein that leads to autonomous activation of cAMP production in end organs, but not at the level of the hypothalamic-pituitary axis. In the gonads, this activation leads to the sporadic development of functional ovarian cysts which lead to episodic uninhibited sex steroid production (estradiol) and precocious puberty where levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) remain low, do not exhibit the nocturnal peak and are not responsive to gonadotropin-releasing hormone (GnRH) analogue therapy. The current treatment for MAS consists of testolactone (an aromatase inhibitor) in combination with spironolactone (an androgen receptor blocker) where efficacy and compliance have been the main reported problems.
Few reports have been published on the use of tamoxifen citrate in children including MAS, pubertal gynecomastia, malignant gliomas, growth hormone secretion and suppression of estrogen action. The safety profile of NOLVADEX in girls is not well established.
Tamoxifen citrate is a nonsteroidal antiestrogen that has both potent antiestrogenic and weakly estrogenic properties. The antiestrogenic effect occurs by competitive inhibition at the level of the estrogen receptor.

Clinical study # 6157US/0013- MAS

Potential benefits: No serious drug-related adverse events were observed in the single, multicenter trial with Nolvadex 20 mg once a day in pediatric patients with MAS. In the 1-year trial of 28 MAS patients aged 2-10 years (22 completed the study), the majority of subjects with vaginal bleeding (67%) during pre-study had a 50-100% reduction in bleeding episodes. Further, a reduction (77%) in bone age maturation rate and in growth rate (60%) were also noted. There were 6/28 complete responders, 18/28 partial responders and 4/28 non-responders.

Potential risks: The majority of the risks associated with NOLVADEX involve the tolerability of the dose (20 mg/day). Most common adverse events included in the following descending order: pharyngitis, rhinitis, headache, fever, abdominal pain, bacterial infection, pathological fracture, increased cough and otitis media.

Effects on the uterus and ovaries: The majority of subjects had asymmetric fluctuations in ovarian size resulting from episodic asymmetric cyst formation. As a result, an elevation in both serum estradiol and estrone were seen periodically in the majority of patients throughout the study. The mean uterine volume following 12 months

of therapy, although increased, remained within the mean uterine volume for pubertal girls.
The risk of endometrial cancers has not been assessed for young patients with MAS but would be predictable based on the pharmacological effect of tamoxifen citrate.
Effects on the liver: In the pediatric trial 6157US/0013, 1 patient had elevated AST and ALT levels which falls within the expected effects of tamoxifen citrate on the liver.
Thromboembolic effects: Tamoxifen has been associated with an increased risk of thromoembolic events. No data in the pediatric population is available.
Ocular disturbances: An increased incidence of ocular disturbances has been seen in patients receiving tamoxifen citrate. No data in the pediatric population is available.

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Pharmacology recommends approval of this drug for the proposed indication. However, no long term data exist on the effects on the reproductive organs, liver or bones of treated pediatric subjects.

B. Recommendation for Nonclinical Studies

The preclinical studies are adequate to support safety for 10 and 20 mg/day and no further preclinical studies are recommended.

C. Recommendations on Labeling

Labeling for the previously approved indication has been amended to include female pediatric patients with MAS. Since there are no new preclinical data, no changes in the fertility, mutagenicity, carcinogenicity or pregnancy sections of the label are necessary.

Special Populations- Pediatric patients
The pharmacokinetics of tamoxifen and N-desmethyl tamoxifen in female pediatric patients showed a small decrease in clearance compared to female breast cancer patients. No difference in exposure to metabolites was noted between the 2 populations. However, among the youngest cohort of pediatric subjects, the C_{max} and AUC values were much higher than those seen in breast cancer patients.

Female children under the age of 2 years and older than 10 years of age should not take NOLVADEX due to lack of studies on these populations. NOLVADEX has not been studied in pediatric male patients.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings

Preclinical studies included toxicology studies in mice, rats, dogs, rabbits and marmosets with duration ranging from single acute doses to 15 months, 2-year carcinogenicity studies in rats, genotoxicity studies, reproductive toxicity studies in rats and rabbits, and special toxicology studies (ocular toxicity in

rats). All these studies have been reviewed under NDA 17-970 for the breast cancer indication of tamoxifen.

B. Nonclinical Safety Issues Relevant to Clinical Use

Exposure comparisons for all preclinical studies were calculated based on body surface area (mg/M^2).

In the **3-month rat** study, reproductive organ (ovaries, testes, seminal vesicles and ventral prostate) showed a reduction in weight at all dose levels (2, 20, 100 mg/kg/day) representing 1, 10 and 50 times drug exposures achieved with the maximum recommended human dose (MRHD) of 20 mg/day. In females, the fibrous endometrial stroma and follicular cysts were seen at the lowest dose of treated animals. Changes in the endometrium and ovaries were progressive following the recovery period of 10 months.

In the **3-month dog** study, animals were dosed with 1 or 10 mg/kg/day for 3 months or 50 mg/kg/day for 2 months followed by 75 mg/kg/day for 1 month. A decrease in weight gain was seen among high dose females. Reproductive systems were affected in all treated dogs and included atrophied testes, reduced ovarian follicles, and a dose-dependent decrease in spermatozoa in all treated males. These effects were seen at 1, 10 and 50 mg/kg which represent 2, 16 and 81 times drug exposures achieved with the MRHD of 20 mg/kg/day.

In the **15-month mouse** study, mice were fed 0, 5 or 50 mg/kg for 3 months followed by reduced levels thereafter (0, 0.05% and 0.005%, respectively for 12 months). The study was stopped at 15 months due to the appearance of skeletal abnormalities represented by spinal deformity with kyphosis (kinky ribs with excessive curvature of the spine backwards). These exposures represent 0, 1 and 12 times drug exposure obtained with the MRHD of 20 mg/kg/day. Treated mice showed a significant increase in endocrine tumors (72%, 44/61 of total tumors) in both immature and mature mice; these included granuloma cell ovarian tumors and interstitial cell testicular tumors. Treated females that did not develop any tumor had atrophied ovaries.

In the **2-year rat carcinogenicity study**, rats were administered 5, 20 or 35 mg/kg/day producing drug exposures of 2, 10 and 17 times those achieved with the MRHD of 20 mg/day. A drug-related increase in hepatocellular carcinomas was seen in all treated groups resulting in animal death in both the mid dose and high dose groups (69% compared to 14% in controls). A statistically significant decrease in spontaneous tumors of the parathyroid, mammary and pituitary glands was observed in all treated groups.

III. ADMINISTRATIVE

A. Reviewer signature: Wafa Harrouk, Ph.D.

B. Supervisor signature: Jeri El Hage, Ph.D.

Concurrence

Non-Concurrence -
(see memo attached)

cc: NDA Arch
HFD 510
HFD 510/MJhonson/Harrouk/ElHage

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Wafa Harrouk
7/10/02 05:32:32 PM
PHARMACOLOGIST

Jeri El Hage
7/11/02 11:05:42 AM
PHARMACOLOGIST