CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-310

PHARMACOLOGY REVIEW(S)

11/14/08

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-310**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**0/0/08**
PRODUCT:	**Casodex (bicalutamide)**
INTENDED CLINICAL POPULATION:	Not seeking indication-response to written request
SPONSOR:	**AstraZeneca**
DOCUMENTS REVIEWED:	**eCTD**
REVIEW DIVISION:	**Division of Metabolism & Endocrinology Products**
PHARM/TOX SUPERVISOR:	**Davis-Bruno**
DIVISION DIRECTOR:	**Parks**
PROJECT MANAGER:	**J. Johnson**

Date of review submission to Division File System (DFS): 11/08

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: N/A sponsor seeking pediatric exclusivity in response to a written request. Clinical study provided in pubertal boys with testotoxicosis and gonadotropin independent precocious puberty.

B. Recommendation for nonclinical studies-N/A

C. Recommendations on labeling-N/A

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings- The animal data presented in this application as well as with other related products demonstrates a clear risk for reproductive and potential skeletal adverse effects. The adverse effects on spermatogenesis are partially recoverable after extended treatment withdrawal periods. The animal data can only assess the potential risk and not the benefit of treatment of testotoxicosis with bicalutamide and anastrozole because the animal models used for the investigation have normal steroidogenesis, in contrast to the clinical subjects.

B. Pharmacologic activity- Bicalutamide is a non-steroidal anti-androgen. It is used in combination with an armomatase inhibitor (anastrozole) to block testosterone activity and prevent aromatization of excess androgen to estrogen.

C. Nonclinical safety issues relevant to clinical use- the sponsor isn't seeking an indication for testotoxicosis although combination use occurs off-label. However effected boys begin pubertal development by 2-3 yrs. of age resulting in rapid growth and bone maturation, progressive virilization and premature epiphyseal fusion and short stature in adulthood.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-310
Review number: 2
Sequence number/date/type of submission:
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: AstraZeneca
Manufacturer for drug substance: same

Reviewer name: Karen Davis-Bruno
Division name: DMEP
HFD #: 510
Review completion date: 11/08

Drug:

Trade name: Casodex
Generic name: bicalutamide
Code name: AZD7054 Casodex; AZD1033 Arimadex (anastrozole)

Relevant INDs/NDAs/DMFs: bicalutamide INDs 29,993, —— 61,238; NDA 20-498 b(4)
Anastrozole: INDs 39,309, —— NDAs 20-541, 22-214

Drug class: non-steroidal anti-androgen
Anastrozole is an aromatase inhibitor

Intended clinical population: pubertal boys with testotoxicosis & gonadotropin independent precocious puberty although sponsor isn't seeking an indication for such Pediatric Exclusivity request only

Clinical formulation: tablets

Route of administration: oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval are owned by or are data of AstraZeneca. Any information or data necessary for approval that the sponsor does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's

approved labeling. Any data or information described or referenced below from a previously approved application that the sponsor does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval.

Studies reviewed within this submission: 90-day juvenile rat tox study

Studies not reviewed within this submission: male fertility studies for bicalutamide (TGR/1291) and anastrozole (TGR/3192) which were previously reviewed under NDA 20-498 and the arimadex NDA 20-541.
Note: For NDA reviews, all section headings should be included.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Bicalutamide is a non-steroidal anti-androgen. Bicalutamide is a racemic mixture of R and S-enantiomers with anti-androgenic activity residing almost exclusively in the R-enantiomer. The R-isomer accounts for 99% of the total circulating drug in man with an elimination half life of 7 days.

Bicalutamide is used in combination with an aromatase inhibitor to block testosterone activity and prevent aromatization of excess androgen to estrogen. Aromatase inhibitors block aromatase, a microsomal P450 enzyme product of the CYP19 gene which converts testosterone to estradiol and androstenedione to estrone. Enzyme activity is present in multiple tissues including the ovary, breast, brain, muscle, liver and adipose tissue. The newest generation of aromatase inhibitors including anastrozole, letrozole and exemestane are potent achieving significant reductions in estradiol with >97% tissue aromatase inhibition.

2.6.2.3 Secondary pharmacodynamics

2.6.2.4 Safety pharmacology

2.6.2.5 Pharmacodynamic drug interactions

2.6.3 PHARMACOLOGY TABULATED SUMMARY

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary
Plasma levels of bicalutamide and anastrozole were measured in the 90-day juvenile rat study; however the sponsor did not provide the calculated exposure data. There were some control animals that had detectable levels of drug during the study however the levels were much lower than the lowest dose group. The sponsor indicates that administration of the combination of drugs did not interfere with the pharmacokinetics of either drug.

2.6.4.2 Methods of Analysis

2.6.4.3 Absorption

2.6.4.4 Distribution

2.6.4.5 Metabolism

2.6.4.6 Excretion

2.6.4.7 Pharmacokinetic drug interactions

2.6.4.8 Other Pharmacokinetic Studies

2.6.4.9 Discussion and Conclusions

2.6.4.10 Tables and figures to include comparative TK summary

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary
Bicalutamide
General toxicology: Bicalutamide experience is extensive in adult males over a 10-600 mg dose range. This application contains the pediatric clinical trial experience. Bicalutamide (Casodex) and anastrozole (Arimadex) are marketed products in the US. Experience with anastrozole is extensive where a 1 mg dose is sufficient to block conversion of testosterone to estradiol in males with comparable sex hormone levels to patients with testotoxicosis. The elimination half life is 40-50 hrs for anastrozole. Pediatric experience with anastrozole was provided by three clinical trials in NDA 22-214 in response to a written request for 1 mg tablets.

The toxicology programs to support the approved adult use of bicalutamide and anastrozole have been limited to evaluation of orally administered drug to adult dogs and rodents. The approved clinical usage of bicalutamide and anastrozole is prostate cancer in males and breast cancer in postmenopausal women respectively. A 3-month juvenile

rat toxicity study in males only, from weanling to sexual maturity was requested by FDA to address the potential effects of the combination.

Reproductive toxicology: Changes in reproductive and some endocrine organs, which are attributed to the pharmacology of bicalutamide, were observed in adult rats and dogs after chronic dosing. Atrophy of seminiferous tubules is a predicted effect with anti-androgens. Reversal of the testicular atrophy occurred after 4 months drug withdrawal in the rat but recovery wasn't observed after 24 weeks drug withdrawal in the dog. Younger animals appear to recovery more rapidly than older animals. Bicalutamide administration should be assumed to produce a period of infertility or reduced fertility during and after treatment. Likewise bicalutamide would be expected to suppress spermatogenesis when given to young males with testotoxicosis, although in reality spermatogenesis has rarely been initiated at the age of initiation of treatment. The 90-day juvenile rat study with the combination of bicalutamide and anastrozole supports that discontinuation of drug treatment during early adolescence might allow normal spermatogenesis to occur at puberty.

Carcinogenicity: Leydig cell hyperplasia was observed in both rats and dogs. Induction of benign Leydig cell tumors in bicalutamide treated male rats and uterine carcinomas in female rats given high doses for 2-years were attributed to prolonged anti-androgenic activity.

A 2-year carcinogenicity study in mice showed an increased incidence of hepatocellular carcinomas in the male mice given 75 mg/kg/day compared to controls. These hepatic tumors were attributed to induction of cytochrome P450 enzymes. However no hepatocellular neoplasias were observed in rats. Bicalutamide has a negative genetic toxicity test battery.

Thyroid hyperplasia and benign thyroid follicular adenoma formation was found in bicalutamide treated rats. This tumor was shown to be a secondary effect of mixed function oxidase induction leading to increased thyroid hormone clearance, and subsequent TSH stimulation of the thyroid gland. However no thyroid tumors were observed in mice where significant induction of hepatic enzymes were evident.

Anastrozole

In multiple dose rat studies at 5 mg/kg/day, reversible body weight and food consumption changes were seen in females and to a lesser extent in males. Reproductive changes related to the pharmacological activity of anastrozole were seen in females at all doses. Hepatocyte hypertrophy related to enzyme induction was seen at all doses in both sexes and an increase in the incidence of chronic progressive glomerulonephropathy was seen in rats (HD=50 mg/kg/day).

In dogs anastrozole was not well tolerated at 12 mg/kg/day for a month resulting in severe body weight loss as well as death. At 8 mg/kg/day longer duration studies of 6 and 12 months were conducted. Liver enlargement generally accompanied by centrilobular hypertrophy was seen at 8 and 12 mg/kg/day were consistent with enzyme

induction. Reversible hepatotoxicity, characterized by multifocal degeneration/necrosis was seen at the 8 mg/kg/day in the 6 month but not the 12 month study. Reproductive findings in both sexes were observed as well as a reduction in R-wave amplitude. Inconsistent R-wave amplitude reductions were also observed in all groups including the controls in the chronic study.

Reproductive toxicology:

Adverse reproductive findings were anticipated based on the inhibition of aromatase. Female rat reproductive findings include increases in the numbers of Graafian follicles, follicular cysts and corpora lutea, with increases in gonadotropin secretion and the inappropriate stimulation of the ovaries. Changes in the ovaries of female dogs after 1, 6, 12 months dosing were essentially similar to those seen in the rat; atrophy of the uterus, vagina, and cervix. Reversible Leydig cell hyperplasia, elevated circulating testosterone was observed in dogs given 1 mg/kg/day anastrozole. Leydig cell hyperplasia was observed in the 2 year mouse, but not rat, bioassays. The sponsor suggests that pre-pubescent males, inappropriate gonadotropin mediated Leydig cell stimulation would not be expected. However a period of reduced fertility would be assumed for males during and after anastrozole administration, although this might not be relevant to pre-adolescent males with testotoxicosis.

A reduction in mating was observed in male weanling rats given anastrozole at 50 or 400 mg/kg/day with a reduction in fertility seen at the highest dose. These adverse effects on mating and fertility were recoverable by the end of the 9-week withdrawal period. A reduction in embryonic survival along with an increase in pre-implantation loss was evident in the high dose group after the first cohabitation which also showed recovery following the 9-week drug withdrawal.

Carcinogenicity: Standard 2-year bioassays have been performed in rats and mice with anatrozole. Increased incidence of hepatocellular adenoma/carcinoma and uterine stromal polyps have been seen in females given 25 mg/kg/day in rats and 50 mg/kg/day in mice. Thyroid adenomas have been observed in male rats given 25 mg/kg/day.
In the mouse, increases n the incidence of benign ovarian epithelial and sex cord stromal granulosa cell tumors occurred at all doses. The incidence of lymphosarcoma was marginally increased in at the high dose at exposure ~45X higher than expected in testotoxicosis patients and are considered a result of non-genotoxic mechanisms associated with either aromatase inhibition or heptic mixed function oxidase induction.

2.6.6.2 Single-dose toxicity

2.6.6.3 Repeat-dose toxicity

2.6.6.4 Genetic toxicology

2.6.6.5 Carcinogenicity

2.6.6.7 Local tolerance

2.6.6.8 Special toxicology studies

90-day Juvenile Male Rat Toxicity with bicalutamide and anastrozole

Key study findings:

- Coadministration of bicalutamide and anastrozole did not effect the TK of either compound
- Coadministration to juvenile male rats resulted in changes in adrenal, epididymis, liver, pituitary, prostate, seminal vesicles, testes and thyroid
- Adverse changes in body weight and food consumption were observed which were reversed during recovery
- HD males were infertile during the treatment phase and recovered after 22-weeks of recovery

Study no.: 0514GR
Volume #, and page #: eCTD 4.2.3.2
Conducting laboratory and location: [ ] b(4)
Date of study initiation: 7/23/03
GLP compliance: yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity:
Formulation/vehicle: ZD7054 in drinking water with 0.5% w/v polysorbate 80; ZD1033 in distilled water
Methods: rats were treated from PND 21, other than standard bone histopathology assessments of BMD or skeletal size were not assessed

Doses: same high and low doses used in the prior 3-month male fertility study and 6-month tox study for bicalutamide and anastrozole

Group (n=20 males/group)	Bicalutamide (mg/kg/d)	Anastrozole (mg/kg/d)
1	0	0
2	10	50
3	250	0
4	0	400
5	250	400

Study design: duration of dosing 91-92 days, duration of post-dose was 170 days, females remained untreated. Assessment of fertility and reproductive function and recovery in males at the HD only.

Results:

2.6.7.7 Repeat-Dose Toxicity | **Report title: 90 Day Oral Toxicity Study in the Juvenile Male Rat with Assessment and Recovery of Reproductive Function. Study number 0514GR** | **Test Article: ZD7054: Bicalutamide ZD1033: Anastrozole**

Daily dose (ZD7054 mg/kg) (ZD1033 mg/L)	ZD7054:0 ZD1033:0 Main test	ZD7054:10 ZD1033:50 Main test	ZD7054:250 Main test	ZD1033:400 Main test	ZD7054:250 ZD1033:400 Main test	ZD7054: 0 ZD1033:0 With-drawal	ZD7054:250 ZD1033:400 With-drawal
Number of animals	**20 M**	**20 M**	**20 M**	**20 M**	**20 M**	**20 M**	**20 M**
ZD1033 (ng/mL) – Day 89, 8 hours light	-	148	NE	1097	827	NE	NE
ZD1033 (ng/mL) – Day 89, 8 hours dark	-	169	NE	629	802	NE	NE
Noteworthy Findings							
Died or Sacrificed Moribund	2 (1 found cannibal-ised; 1 killed for welfare reasons – evidence of misdosing)	3 (1 found dead; 2 killed for welfare reasons – evidence of misdosing)	2 (1 found dead; 1 killed for welfare reasons – evidence of misdosing)	0	3 (2 killed for welfare reasons – evidence of misdosing, 1 found dead)	0	0
Body Weight (%[a,d])	513	-8.2**	-2.5	-18.5***	-14.8***	697	-2.6
Food Consumption (%[a,d])	27	-11**	+3.7	-14.8**	-11.1*	31	+4.9
Water Consumption (%)	22	-22.7	+9.1	-36.4***	-40.9**	-	-
Clinical Observations	-	-	-	-	-	-	-
Ophthalmoscopy	-	-	-	-	-	-	-
Hematology:-							

Daily dose (ZD7054 mg/kg) (ZD1033 mg/L)	ZD7054:0 ZD1033:0 Main test	ZD7054:10 ZD1033:50 Main test	ZD7054:250 Main test	ZD1033:400 Main test	ZD7054:250 ZD1033:400 Main test	ZD7054: 0 ZD1033:0 With-drawal	ZD7054:250 ZD1033:400 With-drawal
Number of animals	**20 M**	**20 M**	**20 M**	**20 M**	**20 M**	**20 M**	**20 M**
Haemoglobin (g/dL)	15.3	15.3	15.2	14.9	14.6**	15.7	15.4*
Haematocrit (L/L)	0.469	0.468	0.466	0.449*	0.445**	0.477	0.464*
Red Blood Cell Count (10^12/L)	8.8	8.8	8.8	8.4**	8.5*	9.0	8.7*
Reticulocytes (10^9/L)	265	237*	260	233**	239*	242	258
Red Cell Distribution Width %	13.2	12.1***	12.9	12.1***	12.2***	14.7	14.0
Neutrophils (10^9/L)	1.59	1.15*	1.00***	1.06**	1.10**	1.45	2.58**
Lymphocytes (10^9/L)	5.75	5.55	5.86	5.59	6.49*	4.34	4.74
Serum Chemistry:-							
Cholesterol (mmol/L)	2.3	2.5	2.4	2.5	3.0***	3.1	3.5*
Total protein (g/L)	68	71**	69	68	72***	71	72
Triglycerides (mmol/L)	1.65	1.17**	0.93***	0.78***	0.79***	1.00	0.96
Alkaline phosphatase (IU/L)	106	85***	79***	90**	82***	80	101*
Hormone Assessment:-							
Rat follicle stimulating hormone (ng/mL)	8.6	11.9*	15.9***	9.2	17.1***	5.0	7.5***
Rat lutenising hormone (ng/mL)	1.12	1.57	3.01**	1.30	2.41**	1.13	1.22
Inhibin B (pg/mL)	69	89	69	75	89	35	26*

Daily dose (ZD7054 mg/kg) (ZD1033 mg/L)	ZD7054:0 ZD1033:0	ZD7054:10 ZD1033:50	ZD7054:250	ZD1033:400	ZD7054:250 ZD1033:400	ZD7054: 0 ZD1033:0	ZD7054:250 ZD1033:400
	Main test	Main test	Main test	Main test	Main test	With-drawal	With-drawal
Number of animals	20 M	20 M	20 M	20 M	20 M	20 M	20 M
Testosterone (nmol/L)	7.5	4.9	7.8	1.7**	8.8	3.3	2.8
Balanopreputial separation Day of study first observed/Day of study last observed	[b]/31	39/48	46/60	[b]/31	52/59	[b]/[b]	53/64
Fertility index % main test	100	NE	NE	NE	0	NE	NE
Fertility index % 1st pairing withdrawal phase	NE	NE	NE	NE	NE	95	79
Fertility index % 2nd pairing withdrawal phase	NE	NE	NE	NE	NE	95	95
Copulation index % main test	60	NE	NE	NE	20	NE	NE
Copulation index % 1st pairing withdrawal phase	NE	NE	NE	NE	NE	95	95
Copulation index % 2nd pairing withdrawal phase	NE	NE	NE	NE	NE	100	100
Pre-coital interval (days) main test	1.0	NE	NE	NE	0	NE	NE
Pre-coital interval 1st pairing withdrawal phase	NE	NE	NE	NE	NE	2.2	2.1
Pre-coital interval 2nd pairing withdrawal phase	NE	NE	NE	NE	NE	2.7	2.4
Number of implantations – main test	14	NE	NE	NE	0	NE	NE
Number of live embryos – main test	12	NE	NE	NE	0	NE	NE

Daily dose (ZD7054 mg/kg) (ZD1033 mg/L)	ZD7054:0 ZD1033:0	ZD7054:10 ZD1033:50	ZD7054:250	ZD1033:400	ZD7054:250 ZD1033:400	ZD7054: 0 ZD1033:0	ZD7054:250 ZD1033:400
	Main test	Main test	Main test	Main test	Main test	With-drawal	With-drawal
Number of animals	20 M	20 M	20 M	20 M	20 M	20 M	20 M
Pre-implantation loss (%) – main test	7.1	NE	NE	NE	0	NE	NE
Post implantation loss (%) – main test	13.1	NE	NE	NE	0	NE	NE
Number of implantations – 1st pairing withdrawal phase	NE	NE	NE	NE	NE	14	12
Number of live embryos – 1st pairing withdrawal phase	NE	NE	NE	NE	NE	13	11
Pre-implantation loss (%) – 1st pairing withdrawal phase	NE	NE	NE	NE	NE	22.4	16.0
Post implantation loss (%) – 1st pairing withdrawal phase	NE	NE	NE	NE	NE	6.4	21.6
Number of implantations – 2nd pairing withdrawal phase	NE	NE	NE	NE	NE	12	12
Number of live embryos – 2nd pairing withdrawal phase	NE	NE	NE	NE	NE	11	11
Pre-implantation loss (%) – 2nd pairing withdrawal phase	NE	NE	NE	NE	NE	16.1	18.9
Post implantation loss (%) – 2nd pairing withdrawal phase	NE	NE	NE	NE	NE	15.3	9.4

Daily dose (ZD7054 mg/kg) (ZD1033 mg/L)	ZD7054:0 ZD1033:0	ZD7054:10 ZD1033:50	ZD7054:250	ZD1033:400	ZD7054:250 ZD1033:400	ZD7054: 0 ZD1033:0	ZD7054:250 ZD1033:400
	Main test	Main test	Main test	Main test	Main test	With-drawal	With-drawal
Number of animals	20 M	20 M	20 M	20 M	20 M	20 M	20 M
Organ Weights (%)							
Adrenal glands – absolute	0.059	-3.4	+42.4***	-10.2	+22.0	0.055	+9.09
relative	0.012	0.0	+41.7***	+8.3	+41.7***	0.008	+12.5
Epididymides – absolute	1.253	-38.0***	-49.1***	-18.4***	-55.6***	1.337	-2.92
relative	0.248	-32.3***	-47.6***	+0.4	-48.0***	0.195	-0.51
Kidneys – absolute	2.945	-17.5***	-8.9**	-17.4***	-16.1***	3.636	+0.77
relative	0.582	-10.1***	-6.9**	+1.4	-1.7	0.527	+3.80
Liver – absolute	18.985	-5.1	+6.6	-4.6	+10.4**	21.466	+7.23
relative	3.741	+3.6	+9.6*	+17.5***	+29.8***	3.127	+9.24
Pituitary gland x1000 – absolute	10.500	+14.8	+29.6**	-2.9	+8.1	11.900	+26.47*
relative	2.077	+25.6	+32.9**	+19.7	+26.0*	1.735	+29.68
Prostate gland – absolute	0.534	-70.0***	-78.5***	-30.0***	-82.6***	0.726	-2.75
relative	0.106	-67.0***	-77.4***	-15.1	-80.2***	0.106	0.00
Testes – absolute	3.642	-5.2*	+0.8	-11.0***	-14.4***	3.771	-10.45**
relative	0.722	+3.2	+3.5	+9.3**	+0.4	0.547	-7.50
Thymus – absolute	0.533	+27.6***	+54.8***	+6.0	+38.6***	0.320	-0.5
relative	0.105	+40.0***	+59.0***	+30.5***	+62.9***	0.046	+4.35
Gross Pathology							

Daily dose (ZD7054 mg/kg) (ZD1033 mg/L)	ZD7054:0 ZD1033:0 Main test	ZD7054:10 ZD1033:50 Main test	ZD7054:250 Main test	ZD1033:400 Main test	ZD7054:250 ZD1033:400 Main test	ZD7054: 0 ZD1033:0 With-drawal	ZD7054:250 ZD1033:400 With-drawal
Number of animals	20 M	20 M	20 M	20 M	20 M	20 M	20 M
Adrenal glands - discolouration	0	2	4	0	8	1	1
Epididymides – mass/nodule	0	1	3	0	3	0	2
Epididymides – small	0	2	9	0	3	0	3
Prostate gland – small	0	15	19	0	20	0	1
Seminal vesicles - small	0	17	18	1	20	0	0
Testes – small	0	0	6	0	2	1	3
Testes – enlarged	0	0	3	0	0	0	0
Thymus- enlarged	0	2	7	1	3	0	0
Histopathology							
Adrenal glands – zona fasciculata vacuolation	0	0	5	0	5	17	19
Adrenal glands – cortical hypertrophy	0	4	4	0	7	0	0
Epididymides - sperm granuloma(ta)	0	12	14	0	8	1	3
Epididymides – exfoliated seminferous epithelial cells	0	2	1	2	14	0	0
Epididymides – absence of spermatozoa	0	2	13	0	3	1	2
Liver – centrilobular hypertrophy	0	1	0	14	8	0	0

Daily dose (ZD7054 mg/kg) (ZD1033 mg/L)	ZD7054:0 ZD1033:0 Main test	ZD7054:10 ZD1033:50 Main test	ZD7054:250 Main test	ZD1033:400 Main test	ZD7054:250 ZD1033:400 Main test	ZD7054: 0 ZD1033:0 With-drawal	ZD7054:250 ZD1033:400 With-drawal
Number of animals	20 M	20 M	20 M	20 M	20 M	20 M	20 M
Liver - necrosis	0	0	0	0	0	17	20
Liver - inflammation	0	0	0	0	0	17	20
Pituitary gland – vacuolated pituicytes	1	11	19	1	20	10	12
Prostate gland – secretion reduced	0	17	19	1	19	1	3
Prostate gland - atrophy	1	0	1	0	8	0	0
Seminal vesicles – secretion reduced	0	20	19	2	20	4	4
Testes – tubular epithelial degeneration - grades 1, 2, 3, 4 or 5	0	14	14	8	18	2	17
Testes – sertoli cell vacuolation	0	3	2	7	15	0	0
Testes – interstitial cell hyperplasia	0	0	14	0	12	0	0
Thyroid gland – follicular cell hypertrophy	0	3	13	2	11	0	0
Thyroid gland – small follicles prominent	0	4	16	1	12	0	0

- = No noteworthy findings; + = Mild; ++ = Moderate; +++ = Marked
* = p<0.05;** = p<0.01; *** = p<0.001 (Student's t test)
a At end of dosing period. For controls, group means are shown, for treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences)
b No previous observations recorded, therefore, balanopreputial separation may have already occurred
c Both absolute and relative weights differed from controls in the direction indicated. Number indicates percent difference for the absolute organ weights.

2.6.6.9 Discussion and Conclusions

Co-administration of bicalutamide and anastrozole to juvenile male rats resulted in changes in the adrenal glands, epididymides, liver, pituitary, prostate, seminal vesicles, testes and thyroid gland. Recovery of these changes was partially reversible in the testes and epididymides and complete in the other effected tissues following the recovery

period. Adverse changes in body weight and food consumption in all dosed groups were observed which were recoverable upon drug withdrawal. Rats given high dose combination were infertile at the end of the main study, but recovery of fertility was evident after 22 weeks of drug withdrawal.

The results of this study with anastrozole differ from those performed with letrozole (Novartis). In the Novartis study under IND — adverse effects of letrozole were seen in decreased body weight, crown to rump length, skeletal changes (decreased and not recoverable in males but increased in females, decreased BMD, delayed sexual maturity and reproductive function, as well as adverse effect on endocrine function. Letrozole was given at 0.003, 0.03, 0.3 mg/kg/day in rats from postnatal day 7 onward. b(4)

In contrast this male juvenile animal study treated with bicalutamide +/- anastrozole (50, 400 mg/kg/day) from postnatal day 21 onward. This developmental difference in treatment time is significant with respect to rat post-natal development between studies as well as the dosage administered. Literature suggests that anastrazole is 2.5X more potent than letrozole in inhibiting total body aromatization and hence inhibition of circulating estrogen in postmenopausal breast cancer patients on a mg basis (Fertility & Sterility 86(3):S121-S122; Sept. 2006). Premenopausal breast cancer patients who underwent ovarian stimulation with anastrozole had a significantly higher exposure to estradiol than those who were stimulated with letrozole (J Clin Endoc & Metabolism 92(6): 2197-220, 2007).

The reproductive effects of aromatase inhibition in males results in less testosterone conversion to estradiol because the aromatase inhibitors bind to the same site as testosterone on aromatase. Administration of aromatase inhibitors in premenopausal women does not significantly decrease estrogen because ovarian aromatase is subject to gonadotropin stimulation and estrogen synthesis escapes inhibition in women with ovarian function. This is why aromatase inhibitors are not effective for breast cancer treatment in women with ovaries unless combined with an agent that will suppress function e.g. gonadotropin releasing agonist or hormone analogues.

Estrogen can prematurely facilitate bone epiphysis closure resulting in decreased growth. Therefore on a mg/kg basis one would anticipate anastrozole; a more potent aromatase inhibitor given at higher doses to result in greater inhibition of circulating estrogen and therefore decreased adverse bone effects due to inhibition of premature closure of the epiphysis in males.

In similar juvenile rat studies with letrozole, dose related effects on bone growth and maturation were noted PND 42-91. The axial and appendicular skeleton of treated males was smaller than controls at the end of treatment with an overall decrease in BMD. Evidence of recovery in size and mass were observed in LD males given 0.003 mg/kg/day, but not in higher dose groups. Bones of females given 0.3 mg/kg/day remained larger than control through recovery and had decreased BMD compared to controls through recovery. Tibial cortical thickness was notably increased for females in the HD group at the end of recovery which was attributed to endosteal bone apposition

following treatment withdrawal. The assessment of skeletal growth and maturation was limited to a single histopathological evaluation of the sternum in study 0514GR with anastrozole.

High dose combination of bicalutamide and anastrozole to juvenile rats caused a delay in puberty as evidenced by balanopreputial separation. This delay was attributable to the anti-androgen effects of bicalutamide as anastrozole treatment alone resulted in successful balanopreputial separation.

Loss of sexual dimorphism of the adrenal cortex especially in the rat is related to hepatic production of corticosteroid binding globulin (CBG). CBG is increased by estrogens and suppressed by androgens, thus anti-androgen treatment should increase CBG levels, reduce free corticosteroid levels and via stimulation of the pituitary-adrenal axis resulting in adrenal cortical enlargement. Although bicalutamide binds weakly to sex hormone binding globulin (SHBG), no binding to CBG was observed. No effects on glucocorticoid and mineralocorticoid status of patients were observed during clinical development. Loss of normal adrenal weight and sexual dimorphism in young rats was also observed with anastrozole, but only in females and a similar decrease in female adrenal weight was observed in the 6-month rat toxicity study.

The majority of animals given low and high dose combination as well as bicalutamide alone show vacuolated pituicytes and reduces prostate and seminal vesicle fluid. This is an expected anti-androgen effect on the pituitary gonadal axis which is limited by exposure of the drug to the CNS. Pituitary gonadoptroph hypertrophy and vacuolation (castration cells) have been observed in male rats in the 6 month toxicology studies. Action at pituitary gonadotrophn androgen receptors causes some increase in LH secretion, accounting for the Leydig cell hyperplasia observed in both rat and dog. Similar changes in LH secretion were observed in the high dose bicalutamide groups in the juvenile rat study, also resulting Leydig cell hyperplasia. Anastrozole had no effect on Leydig cells as evident from 6-month toxicology studies with Armidex.

Hypertrophy of Leydig cells in rats is a consequence of elevated LH stimulation due to disruption of the normal gonadal-pituitary gland negative feedback mechanism. There are no reports of testicular adverse events for prostate cancer patients treated with Casodex in clinical trials.

Tubular epithelial degeneration in the testes occurred with a dose-related severity in animals receiving the combination of bicalutamide and anastrozole. This degeneration is attributable to bicalutamide since this compound alone resulted in extensive tubular change in contrast to the minimal effect seen with anastrozole. Although the severity was somewhat reduced, testicular tubular epithelial degeneration was still present in the majority of animals following recovery. Despite partial recovery, the rats were fertile. A minimal effect was observed with anastrozole confirming the absence of effect on spermatogenesis noted in the Arimidex rat 6- month toxicity and fertility studies.

Sertoli cell vacuolation showed a dose related increase in incidence in the high dose combination group that either constituent alone which may reflect an additive effect of the two compounds.

A high incidence of sperm granulomata was observed in the epididymis of animals that received bicalutamide, either alone or in both the combination groups with anastrozole. Partial recovery was observed at the end of recovery with a reduced incidence of epididymal sperm granulomata (3/20 rats compared to 1/20 controls). Sperm granulomata were also observed in the Casodex 6-month toxicity study in rats, but at a reduced incidence compared to the present juvenile study. This probably reflects a technical difference in tissue processing between the studies as the current juvenile study assessed the whole epididymis compared to the assessment of the caput section only as performed in the 6 month study.

Granulomata are formed when physical rupture of the tubules and ducts release mature spermatozoa into the interstituitum causing an inflammatory reaction possibly stimulated by the fatty acids released by the degenerating spermatozoa. Although anti-androgenic effects on sperm motility, germ cell sloughing and/or testicular fluid flow probably all contribute to the formation of the granulomata. Granulomata formation may be an anti-androgen effect in juvenile rats since and increase in epididymal sperm granulomata formation has also been seen following the 3-week administration of the flutamide; another anti-androgen (Wolfe and Patel 2004). Due to the absence of spermatogenesis in testotoxicosis patients there isn't a concern with bicalutamide administration to young males.

2.6.6.10 Tables and Figures

2.6.7 TOXICOLOGY TABULATED SUMMARY

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Testotoxicosis is a form of gonadotropin-independent (peripheral) precocious puberty in which boys experience early onset and progression of puberty. Patients have accelerated growth, early development of secondary sexual characteristics and usually reduced adult height. Testotoxicosis is caused by an activating mutation of the luteinizing hormone (LH) receptor, leading to increased levels of sex steroids in the context of low LH. Therapy has, therefore, traditionally targeted steroidogenesis. However, the drugs used have been associated with side effects. More recently, off-label use of a combination of an oral anti-androgen and an aromatase inhibitor decreased height velocity and improved predicted height.

Given the marked perturbation of testicular function and endocrine disruption seen in testotoxicosis the anticipated adverse effect on fertility revealed by this juvenile rat study,

and confirm the data from the adult rat may not preclude therapeutic use of the drug combination. The body of animal data may have limited relevance on the proposed pediatric use in testotoxicosis because the extent and duration of the estrogen deficiency is quite different in the animal models compared to the clinical situation. Rodent pre-pubescence is quite short unlike the extended latency of testicular quiescence in human males. This species difference coupled with the need to regulate the perturbed steroidogenesis in these young male subjects requires consideration. Unlike the extensive clinical experience with adult cancer indications, treatment with bicalutamide/anastrozole in a limited numbers of in children have been generated. The combination of a status condition of low FDH/LH combined with aromatase inhibition would synergistically decrease gonadotropins which is the intended goal in testotoxicosis. Adequate androgen control can be maintained in an artificial clinical trial setting of short-term duration.

Unresolved toxicology issues: none

Recommendations: The animal data presented in this application as well as with other related products demonstrates a clear risk for reproductive and potential skeletal adverse effects. The adverse effects on spermatogenesis are partially recoverable after extended treatment withdrawal periods. The animal data can only assess the potential risk and not the benefit of treatment of testotoxicosis with bicalutamide and anastrozole because the animal models used for the investigation have normal steroidogenesis, in contrast to the clinical subjects. The sponsor isn't seeking an indication for testotoxicosis although combination use occurs off-label. Effected boys begin pubertal development by 2-3 yrs. of age resulting in rapid growth and bone maturation, progressive virilization and premature epiphyseal fusion and short stature in adulthood.

Suggested labeling: N/A

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/s/

Karen Davis-Bruno
11/14/2008 02:17:44 PM
PHARMACOLOGIST