CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-310

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

12/15/08

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-310	Submission Date(s): 06/25/08
Brand Name	Casodex®
Generic Name	Bicalutamide
Reviewer	Ritesh Jain, Ph.D.
Team Leader	Sally Choe, Ph.D.
OCP Division	Clinical Pharmacology -2
OND division	Metabolic and Endocrine Products
Sponsor	AstraZeneca
Submission Type; Code	Type 6 NDA (Pediatric Exclusivity); Priority
Formulation; Strength(s)	Oral dispersible Tablets, Casodex® in combination with Arimidex®
Indication	Treatment of male pubertal patients with testotoxicosis.

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CASODEX® (bicalutamide) is an anti-androgenic agent commonly used for prostrate cancer. ARIMIDEX® (anastrozole) is a potent and selective nonsteroidal aromatase inhibitor indicated for the treatment of early and advanced breast cancer in postmenopausal women. The purpose of this application is to provide safety, efficacy and pharmacokinetic information on the use of Casodex (bicalutamide) in combination with Arimidex (anastrozole) in male pubertal patients with testotoxicosis. Testotoxicosis is a form of gonadotropin-independent (peripheral) precocious puberty, in which boys experience early onset (2-3 years age) and progression of puberty. Testotoxicosis is caused by luteinizing hormone (LH) receptor mutation leading to increased levels of sex steroids. Affected boys usually begin early pubertal development resulting in rapid growth and bone maturation, progressive virilization and ultimately, premature epiphyseal fusion and short stature in adulthood.

The studies in this submission are conducted in response to FDA's original Pediatric Written Request (WR) dated 04/17/2003 to obtain safety, efficacy and pharmacokinetic information of Casodex in pediatric patients with testotoxicosis. Six amendments have been made on the original WR and pediatric exclusivity was granted on 09/19/2008. No indication is being sought in this application and the clinical efficacy trial failed to meet the primary efficacy endpoint and no indication is being sought in this application by the sponsor. Please see the review by the medical officer, Dr. Dragos Roman for details. The sponsor proposes that appropriate sections of the CASODEX label should be updated to include data from the studies submitted.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 (OCP/DCP-2) has reviewed NDA 22-310 submitted on 04/17/2003 and finds it acceptable. Recommendation and labeling comments should be conveyed to the sponsor as appropriate.

1.2 PHASE IV commitments

Not applicable.

1.3 SUMMARY of Important Clinical Pharmacology AND BIOPHARMACEUTICS Findings

The studies submitted in this application are based on FDA's Pediatric Written Request (WR) Amendment #6 dated 05/08/2008 to obtain safety, efficacy, and pharmacokinetic information on the use of Casodex in combination with Arimidex in pediatric patients with testotoxicosis. This application contained a total of three studies; two relative oral bioavailability studies investigating the relative bioavailability between the pediatric dispersible tablet formulation and market oral tablets of bicalutamide and anastrozole in healthy adult volunteers and the third clinical study investigating the safety and efficacy of bicalutamide and anastrozole when given together in patients (14 enrolled, 13 completers) with testotoxicosis.

After single dose administration to fasted healthy adult subjects, plasma concentrations of R-bicalutamide (active isomer) after dispersible tablets (2 X 25 mg) administration were comparable to those of the marketed (50 mg) tablet. The relative bioavailability of the dispersible tablet to the marketed tablet was 0.93 (90% CI: 0.89 – 0.96) from comparison of AUC and 0.92 (90% CI: 0.90 – 0.94) from comparison of C_{max}.

Table 1: Statistical comparison of primary pharmacokinetics parameters for R-bicalutamide after oral administration of marketed CASODEX tablet and 2 X 25 mg dispersible tablet

Variable	Dispersible 2 x 25 mg tablets glsmean	Marketed 50 mg tablet (CASODEX) glsmean	Relative bioavailability	90% CI lower limit	90% CI upper limit
AUC (ng.h/mL)	187956.73 (n=29)	202893.04 (n=27)	0.93	0.89	0.96
C_{max} (ng/mL)	792.90 (n=30)	863.18 (n=29)	0.92	0.90	0.94

AUC, area under the plasma concentration-time curve from zero to infinity
CI, confidence interval
Cmax, maximum plasma concentration
glsmean, geometric least squares mean

Also, plasma concentrations of anastrozole were comparable after administration of the marketed and dispersible tablets (1 mg) to fasted volunteers. The relative bioavailability, as assessed by the ratios of the dispersible tablet to the marketed tablet was 0.98 (90% CI: 0.96 – 1.01) from comparison of AUC and 0.98 (90% CI: 0.94 – 1.02) from comparison of C_{max}.

Table 2: Statistical comparison of primary pharmacokinetics parameters for Anastrozole after oral administration of marketed 1 mg ARIMIDEX tablet and 1 mg dispersible tablet

Variable	1 mg dispersible tablet glsmean[a] (N = 28)	1 mg marketed tablet glsmean[a] (N =28)	Relative bioavailability	90% CI lower limit	90% CI upper limit
AUC (ng.h/mL)	638.35	648.87	0.984	0.962	1.006
C_{max} (ng/mL)	12.15	12.46	0.975	0.935	1.017

[a] Geometric least squares mean
CI = confidence interval

The primary efficacy variable in clinical efficacy study is change in growth rate (cm/year) after 12 months of treatment with bicalutamide and anastrozole. The clinical

efficacy trial failed to meet the primary efficacy endpoint and no indication is being sought in this application by the sponsor. Please see the review by the medical officer, Dr. Dragos Roman for details.

2. QBR

2.1 General Attributes

2.1.1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and Biopharmaceutics of the drug?

The studies in this submission are conducted in response to FDA's original Pediatric Written Request (WR) dated 04/17/2003 to obtain safety, efficacy and pharmacokinetic information of Casodex in pediatric patients with testotoxicosis. Six amendments have been made on the original WR (See Appendix for WR). The written request from the FDA required the sponsor to conduct 3 studies to obtain 6-month pediatric exclusivity for CASODEX (bicalutamide) tablets. The current application provides data from these studies.

Study 1: A relative bioavailability (BA) study between a pediatric bicalutamide orodispersible tablet formulation and the marketed 50 mg bicalutamide oral tablet in adults. (Study # D6873C00003)

Study 2: A relative BA study between a pediatric anastrozole orodispersible tablet formulation and the marketed 1 mg anastrozole oral tablet in adult (Study # D6873C00002).

Study 3: An efficacy and safety study of bicalutamide when used in combination with anastrozole for the treatment of precocious puberty in boys with testotoxicosis (Study # D6873C00047)

2.1.2. What is the mechanism of action and therapeutic indication?

Testotoxicosis is caused by luteinizing hormone (LH) receptor mutation leading to increased levels of sex steroids. The changes seen in testotoxicosis are driven by actions of both androgen and estrogen. Casodex (bicalutamide) is an oral non-steroidal anti-androgenic that competes with intra-cellular testosterone and dihydrotestosterone (DHT) for nuclear androgen receptor binding sites in the target cell. Bicalutamide may assist in the management of testotoxicosis by blocking androgen induced growth and development of secondary sexual characteristics. Casodex is currently indicated for patients with prostrate cancer.

Arimidex (Anastrozole) is a potent and selective nonsteroidal aromatase inhibitor. Aromatase inhibitors are a class of compounds that act systemically to inhibit estrogen synthesis in tissues thereby reducing estrogen production. These compounds prevent synthesis by inhibiting the enzyme aromatase, which catalyzes the conversion of the adrenal androgens, androstenedione and testosterone to the estrogens, estrone and estradiol respectively. Anastrazole may suppress the estrogen level in boys with

testotoxicosis. Anastrozole in indicated for the treatment of early and advanced breast cancer in postmenopausal women.

No indication is being sought in this application.

2.1.3. What are the proposed dosage and route of administration?

No indication is sought in this study. However, the clinical efficacy and safety study used once-daily oral anastrozole (ARIMIDEX™) orodispersible tablets and bicalutamide (CASODEX™) orodispersible tablets. Study medication was independently titrated in the following ascending doses:

- dispersible bicalutamide 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg
- dispersible anastrozole 0.5 mg, 1 mg, 2 mg, 4 mg, 8 mg

The dosing of anastrozole and bicalutamide was independently tailored for each patient. Anastrozole and bicalutamide dose revisions were driven by serum estradiol and plasma bicalutamide concentrations, respectively. Doses of each drug were iteratively adjusted until a dose was reached that gave steady-state trough serum estradiol concentrations of <10 pmol/L (2.7 pg/mL) and R-bicalutamide (the active isomer of bicalutamide) trough plasma concentrations within the range 5-15 μg/mL. Anastrozole dose escalation was stopped once a plasma anastrozole concentration of 350 ng/mL or a daily dose of 8 mg was reached.

2.1.4. What is the rationale to select the dosage for Casodex and Arimidex?

Clinical data in adults with prostrate cancer have shown that CASODEX at a dose of 50 mg daily provides effective androgen receptor blockade as demonstrated by significant falls in prostate specific antigen (PSA) and improvement in clinical outcome occurring with Casodex usage at this dose. The plasma mean plasma concentration of bicalutamide after daily 50 mg single dose administration to adult males was observed to be 10 μg/mL, with a typical range of 5- 15 μg/mL. Since the exposure of 5-15 μg/mL is shown to be effective in having anti-androgenic effect in adults, this exposure window was also chosen for pediatric patients with testotoxicosis. The starting dose of Casodex was 12.5 mg, with dose being titrated up to 150 mg based on observed plasma R-bicalutamide concentrations on Day 21 or later.

Boys with testotoxicosis were expected to have elevated serum estradiol concentrations because of the conversion of excess testosterone to estradiol. Dose selection and titration of Arimidex is based on the plasma estradiol concentrations. The plasma estradiol concentrations were kept below10 pmol/L as this represents the plasma estradiol concentration in boys at early puberty. Anastrozole dose escalation was stopped once a plasma anastrozole concentration of 350 ng/mL or a daily dose of 8 mg was reached.

2.1.5. Is any DSI (Division of Scientific Investigation) inspection requested for any of the clinical studies?

No DSI inspection was requested for any of the studies.

2.2 General Clinical Pharmacology

2.2.1. What is known about the general pharmacology of Casodex and Arimidex?

Refer to original NDA 20-541 approved by FDA on December 27, 1995 for Arimidex and NDA 20-498 approved by FDA on October 4, 1995 for Casodex.

2.2.2. What is the primary measurement of efficacy?

The primary efficacy variable in the clinical efficacy study is change in growth rate (cm/year) after 12 months of treatment with bicalutamide and anastrozole. Efficacy analysis was done by measuring the height of the patients at ≥ 6 months pre-study period, at baseline and after 12 months of treatment. Growth rate at baseline is derived from retrospective data as follows:
GR_B (cm/year) = [height (cm) at baseline – height (cm) at ≥ 6 months pre-study period]/ [time interval in years between baseline and pre-study assessment].

Change in growth rate after 12 months of the treatment can be obtained by difference in the growth after 12 months (GR_{12} cm/year) and growth rate at baseline (GR_B cm/year).

2.2.3. What is the pharmacodynamic response to bicalutamide and anastrozole?

The primary efficacy variable in clinical efficacy study is change in growth rate (cm/year) after 12 months of treatment with bicalutamide and anastrozole. The clinical efficacy trial failed to meet the primary efficacy endpoint. Please see the review by the medical officer, Dr. Dragos Roman for details.

2.2.4. Are the active moieties in the plasma appropriately identified and measured?

Yes.

2.3 Intrinsic Factors

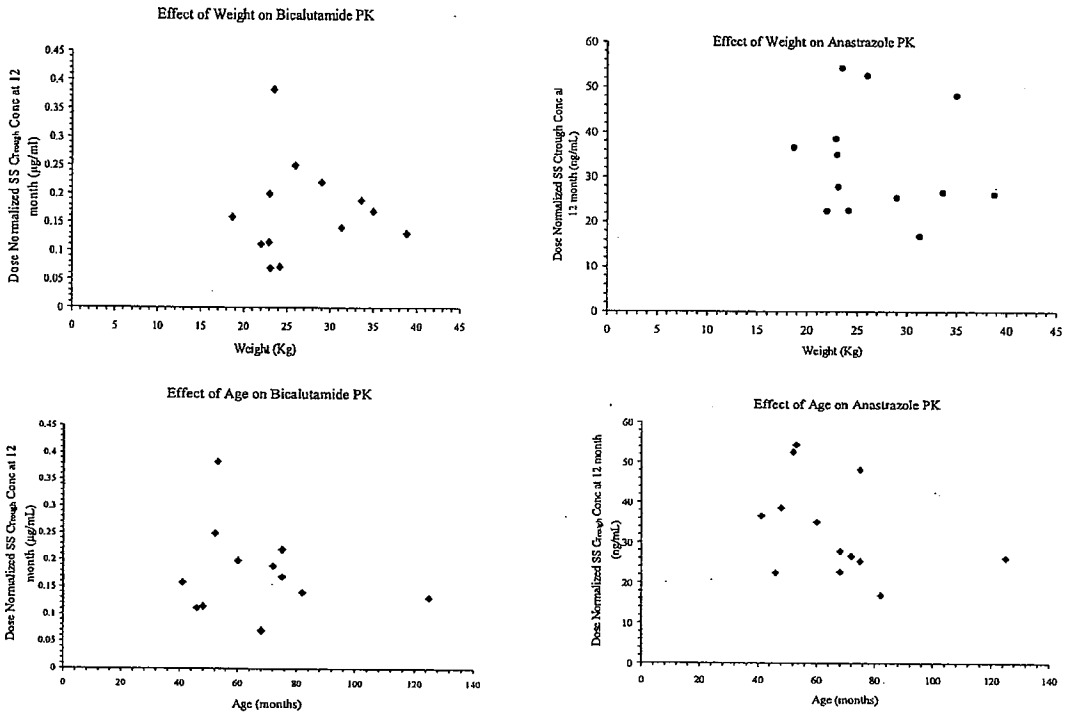
2.3.1. What are the pharmacokinetics characteristics of bicalutamide and anastrozole in pediatric patients?

The mean plasma trough concentrations for R-bicalutamide remained in the pre-specified concentration range of 5-15 μg/mL. For the 13 patients who were stabilized for bicalutamide, (i.e. attained their potential therapeutic dose), 8 patients were on 50 mg, 4 patients on 100 mg, and 1 patient on 12.5 mg bicalutamide. The final stabilized dose for anastrozole was 0.5 mg for 10 patients and 1 mg for 3 patients. The steady-state R-bicalutamide and anastrozole concentrations appeared to be attained in the majority of

patients by Day 21 and Day 8, respectively, following once a day dosing. Please see 4.2.3. Clinical Study Report D6873C000047 for details.

2.3.2. What is the influence of age and weight on PK of bicalutamide and anastrozole in pediatric patients?

No definitive conclusion on the effect of age and body weight on steady state C_{trough} concentrations of bicalutamide and anastrozole can be drawn due to the limited number of sample size. However, in one of the previous reviews of NDA 22-214 by Dr. Manoj Khurana it was found that body weight is an important covariate for the determination of clearance and volume of distribution of anastrozole in pediatric patients.



2.3.3. Is dose proportionality evaluated?

The sponsor claims in their proposed package insert that [

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] Please see 4.2.3. Clinical Study Report D6873C000047 for details.

2.4 Extrinsic factors

Not applicable.

2.5 GENERAL Biopharmaceutics

After single dose administration to fasted healthy adult subjects, plasma concentrations of R-bicalutamide were comparable after administration of the marketed (50 mg) and dispersible tablets (2 X 25 mg). The relative bioavailability of the dispersible tablet to the marketed tablet was 0.93 (90% CI: 0.89 – 0.96) from comparison of AUC and 0.92 (90% CI: 0.90 – 0.94) from comparison of C_{max}. Also, the relative bioavailability for anastrozole, as assessed by the ratios of the dispersible tablet to the marketed tablet was 0.98 (90% CI: 0.96 – 1.01) from comparison of AUC and 0.98 (90% CI: 0.94 – 1.02) from comparison of C_{max}. Thus, the exposure of the two formulations can be considered to be similar.

2.6 Analytical Section

Study D6873C00002: Quantitative assessment of anastrozole concentration in human plasma was conducted employing a validated HPLC-MS/MS method. Samples were extracted using a liquid-liquid extraction procedure. Extracted samples were evaporated to dryness and reconstituted and analyzed by HPLC with an AB/MDS Sciex API 4000 mass spectrometer. The calibration curves were analyzed at anastrozole concentrations of 0.1, 0.250, 1.0, 2.5, 10.0, 25, 50, and 60 ng/mL. The lower limit of quantification (LOQ) for anastrozole was 0.1 ng/mL. Between-batch precision (%CV) results for QC samples prepared at low, medium, and high QC concentrations of anastrozole was less than or equal to 11.0 % and accuracy (%Bias) ranged from -1.0 to -0.4 %. Between-batch precision (%CV) results of the calibration standards of anastrozole were less than 4 % and accuracy (%Bias) ranged from -0.8 to 1.0 %.

Study D6873C00003: Quantitative assessment of R- and S- bicalutamide concentration in human plasma was conducted employing a validated HPLC-MS/MS method. Samples were extracted using a liquid-liquid extraction procedure. Extracted samples were evaporated to dryness and reconstituted and analyzed by chiral HPLC with an AB/MDS Sciex API 4000 mass spectrometer. The calibration curves were analyzed at R- and S-bicalutamide concentrations of 10, 20, 100, 500, 2500, 4500, and 5000 ng/mL. The lower limit of quantification (LOQ) for bicalutamide was 10 ng/mL. Between-batch precision (%CV) results for QC samples prepared at low, medium, and high QC concentrations of R-bicalutamide was less than or equal to 6.8 % and accuracy (%Bias) ranged from -0.8 to -0.3 %. For S-bicalutamide precision (%CV) was less than or equal to 5.4 % and bias ranged from -1.5 to -0.5 %. Between-batch precision (%CV) results of the calibration standards of R-bicalutamide was less than or equal to 3 % and accuracy (%Bias) ranged from -0.8 to 1.6 %. For S-bicalutamide precision (%CV) was less than 3 % and bias ranged from -1.0 to 1.6 %.

Study D6873C000047: Quantitative assessment of anastrozole and R-bicalutamide concentration in human plasma was conducted employing a validated HPLC-MS/MS method (KPV015 and KPV059). R-bicalutamide plasma samples were extracted using a liquid-liquid extraction procedure. Extracted samples were analyzed by chiral HPLC with an AB/MDS Sciex API 4000 mass spectrometer. The calibration curves were

analyzed at R- bicalutamide concentrations of 40, 80, 200, 1000, 5000, 9000, and 10000 ng/mL. The lower limit of quantification (LOQ) for bicalutamide was 40 ng/mL. Between-batch precision (%CV) results for QC samples prepared at low, medium, and high QC concentrations of R-bicalutamide was between 5.9 to 9.8 % and accuracy ranged from 99.5 % to 101.9 %. A between-batch precision (% CV) result of the calibration standards of R-bicalutamide was between 4.5 to 10.7 % and accuracy ranged from 98.7 to 102%.

Anastrozole plasma samples were extracted using a protein precipitation procedure. Extracted samples were analyzed by HPLC with an AB/MDS Sciex API 4000 mass spectrometer. The calibration curves were analyzed at anastrozole concentrations of 1, 2, 5, 10, 50, 100, 250 and 500 ng/mL. The lower limit of quantification (LOQ) for bicalutamide was 1 ng/mL. Between-batch precision (%CV) results for QC samples prepared at low, medium, and high QC concentrations of anastrozole was between 6.1to 8.6 % and accuracy ranged from 99.1 % to 103.2 %. A between-batch precision (% CV) result of the calibration standards of anastrozole was between 2.7 to 9.4 % and accuracy ranged from 98.1 to 101.5%.

24 Page(s) Withheld

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___✓___ Draft Labeling (b4)

_____ Draft Labeling (b5)

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4.2 INDIVIDUAL STUDY REVIEW

4.2.1 Clinical Study D6873C00003

Title: An open-label, randomised, single-centre, cross-over Phase I study to determine the relative bioavailability of bicalutamide 50 mg when administered orally as dispersible tablet and marketed tablet (CASODEX™) in healthy male volunteers.

Investigator and Study Center(s):

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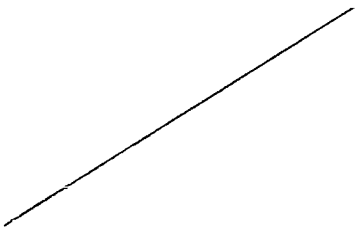
75015 Paris
France

Study Sponsor:

AstraZeneca
Alderley Park
Macclesfield
Cheshire, SK10 4TG, UK

Bioanalytical Analysis:



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STUDY PERIOD: 04 October 2004 (First volunteer enrolled) – 09 March 2005 (Last volunteer completed)

Objective:
The primary objective of this study was to determine the relative bioavailability of bicalutamide when administered as dispersible oral 2 x 25 mg tablets compared with the marketed oral 50 mg tablet (CASODEX) in healthy adult male volunteers.

The secondary objectives of the study were:

- To characterize and compare the pharmacokinetics of bicalutamide 50 mg when administered as dispersible oral tablet and marketed oral tablet (CASODEX) in healthy adult male volunteers

- To ensure the safety of volunteers, and their tolerability to bicalutamide.

Study Design:
This study was a single centre, randomized, open-label, two-period cross-over study in thirty adult male volunteers. The study consisted of two treatment periods (Periods I and II). Each volunteer received two single oral doses of bicalutamide (one in each Period). In Period I volunteers were randomized to receive a single oral dose of either

- 50 mg marketed bicalutamide tablet (CASODEX), or
- 2 x 25 mg dispersible bicalutamide tablets

In Period II volunteers crossed over to receive the formulation not received in Period I. Volunteers were kept in the Clinical Pharmacology Unit (CPU) from the evening before each dose of bicalutamide until at least 48 hours following dosing. The dose was taken at the same approximate time in both periods. In each Period, samples for PK analysis were collected over a 5-week interval. There was a minimum 63-day washout period between doses. Each volunteer returned for a post-study medical examination within the 14 days following the last PK sample in Period II. For each subject, 19 blood samples were withdrawn for the assessment of R- and S-bicalutamide concentrations in plasma over a 5-week period.

Study Population:
Thirty healthy adult male volunteers were enrolled in this study. The mean age of the study population was 48 years (range 36 to 60 years), mean height was 175.7 cm (range 157 to 187 cm) and mean weight was 76.78 kg (range 52.2 to 90.5 kg). The BMI for the study population was 24.82 (range 20.91 to 28.93). All 30 volunteers were nonsmokers at entry to the study.

Bioanalytical Analysis:
Quantitative assessment of R- and S- bicalutamide concentration in human plasma was done employing a validated HPLC-MS/MS method. Samples were extracted using a liquid-liquid extraction procedure. Extracted samples were evaporated to dryness and reconstituted and analyzed by chiral HPLC with an AB/MDS Sciex API 4000 mass spectrometer. The calibration curves were analysed at R- and S-bicalutamide concentrations of 10, 20, 100, 500, 2500, 4500, 5000 ng/mL. The lower limit of quantification (LOQ) for bicalutamide was 10 ng/mL. Between-batch precision (%CV)

results for QC samples prepared at low, medium, and high QC concentrations of R-bicalutamide was less than or equal to 6.8 % and accuracy (%Bias) ranged from -0.8 to -0.3 %. For S-bicalutamide precision (%CV) was less than or equal to 5.4 % and bias ranged from -1.5 to -0.5 %. Between-batch precision (%CV) results of the calibration standards of R-bicalutamide was less than or equal to 3 % and accuracy (%Bias) ranged from -0.8 to 1.6 %. For S-bicalutamide precision (%CV) was less than 3 % and bias ranged from -1.0 to 1.6 %.

Data Analysis:
PK analysis of both R- and S- bicalutamide plasma concentration data was performed by non-compartmental analysis. The relative bioavailability of the dispersible tablet in each individual volunteer was determined from the ratios of the AUC and C_{max} of R-bicalutamide obtained following dosing of the dispersible tablet to the AUC and C_{max} of R-bicalutamide obtained following dosing of the marketed tablet. ANOVA was used to compare the log transformed AUC and C_{max} between the dispersible tablet and marketed tablet. The results were presented in terms of the geometric least square means (glsmeans) for each formulation, the relative bioavailability (i.e. the ratios of glsmeans of dispersible 2 x 25 mg tablets versus marketed 50 mg tablet), and the associated 90% confidence intervals.

There were two protocol deviations, volunteer0017 (took prohibited medication and did not take part in period II) and volunteer0028 (took prohibited medication in period II). So out of 30 volunteers, 28 completed the study and two were withdrawn because of the reasons as described above. Secondary PK parameter were calculated wherever the data allowed. The following pharmacokinetic (PK) variables for both R-bicalutamide and S-bicalutamide were determined: Time to reach the maximum plasma concentration (t_{max}), area under plasma concentration-time curve from zero to time t (AUC_{0-t}), terminal rate constant (λ_z), terminal half-life ($t_{1/2}$), total apparent drug clearance (CL/F), and volume of distribution at steady state (V_{ss}/F).

Pharmacokinetics Results:
The plasma pharmacokinetics of R-bicalutamide following a single oral dose of either a 50 mg marketed tablet (CASODEX) or 2 x 25 mg dispersible tablets was assessed in healthy adult male volunteers. Majority of individuals who completed the study, the R-bicalutamide AUC was well estimated with the extrapolated portion being less than 10%. There were two exceptions, Volunteer 22 on both formulations and Volunteer 28 for the marketed formulation for whom the terminal phase could not be well estimated and thus AUC was not calculable. On these three occasions the percentage AUC extrapolated was considerably higher than other occasions and the terminal phase could not be followed for three times the calculated $t_{1/2}$. For these occasions PK parameters were not reported.

Thus statistical analysis of AUC was completed for 27 on the marketed formulation and for 29 on the dispersible formulation. As C_{max} was estimated for each profile the statistical analysis of C_{max} was completed for 29 on the marketed and 30 on the dispersible formulations respectively.

Plasma concentrations of R-bicalutamide were comparable after administration of the marketed and dispersible tablets to fasted volunteers. The relative bioavailability of the dispersible tablet to the marketed tablet was 0.93 (90% CI: 0.89 – 0.96) from comparison of AUC and 0.92 (90% CI: 0.90 – 0.94) from comparison of C_{max}.

Sponsor's PK analyses for secondary parameters of R-bicalutamide were similar with T_{max} ranging from 9-72 hours, $t_{1/2}$ ranging from 80-124 hours.

Table 1: Primary PK parameters of R-bicalutamide

Variable	Marketed 50 mg tablet (CASODEX)	Dispersible 2 x 25 mg tablets
AUC (ng.h/mL)		
N	27	29
Geometric mean	203900	188100
CV (%)	24.60	20.39
C_{max} (ng/mL)		
N	29	30
Geometric mean	867.8	792.9
CV (%)	16.10	12.58

AUC, area under the plasma concentration-time curve from zero to infinity. AUC could not be estimated for 3 profiles
C_{max}, maximum plasma concentration
CV, coefficient of variation
N, number of volunteers

Table 2: Statistical comparison of primary pharmacokinetics parameters for R-bicalutamide after oral administration of marketed CASODEX tablet and 2 X 25 mg dispersible tablet

Variable	Dispersible 2 x 25 mg tablets glsmean	Marketed 50 mg tablet (CASODEX) glsmean	Relative bioavailability	90% CI lower limit	90% CI upper limit
AUC (ng.h/mL)	187956.73 (n=29)	202893.04 (n=27)	0.93	0.89	0.96
C_{max} (ng/mL)	792.90 (n=30)	863.18 (n=29)	0.92	0.90	0.94

AUC, area under the plasma concentration-time curve from zero to infinity
CI, confidence interval
Cmax, maximum plasma concentration
glsmean, geometric least squares mean

Table 3: Secondary PK parameters for R-bicalutamide

Variable	Marketed 50 mg tablet (CASODEX)	Dispersible 2 x 25 mg tablets
t_{max} (h)		
N	29	30
Median	36.0	48.0
Minimum	9.0	12.0
Maximum	48.0	72.0
AUC_{0-t} (ng.h/mL)		
N	29	30
Geometric mean	204100	188500
CV (%)	26.67	23.75
$t_{½}$ (h)		
N	27	29
Mean	135.2	131.1
SD	26.53	24.97
CL/F (L/h)		
N	27	29
Mean	0.1254	0.1354
SD	0.0362	0.0259
V_{ss}/F (L)		
N	27	29
Mean	24.82	25.70
SD	4.564	3.718

AUC_{0-t} = Area under plasma concentration time curve from zero to the time of the last quantifiable concentration
CL/F = Plasma clearance following oral dosing
CV= Coefficient of variation
N = Number of volunteers
SD = Standard deviation
t_{max} = Time to Cmax
$t_{½}$ = Elimination half-life
V_{ss}/F = Volume of distribution at steady state following oral dosing

Plasma concentrations of S-bicalutamide were appreciably lower than those of R-bicalutamide at all sampling time-points. Beyond 72 hours the S-bicalutamide plasma concentrations fell below the limit of quantification for all profiles and the extrapolated portion of the S-bicalutamide AUC accounted for more than 10% of the total. C_{max} data for S-bicalutamide were only between around 4 – 11% of the corresponding R-

bicalutamide C_{max} values. The plasma concentration-time profile of S-bicalutamide and the range of values for C_{max}, AUC(0-t) and T_{max} S-bicalutamide was comparable between the two formulations.

Table 4: Summary of PK parameters for S-bicalutamide

Variable	Marketed 50 mg tablet (CASODEX)	Dispersible 2 x 25 mg tablets
C_{max} (ng/mL)		
N	29	30
Geometric mean	60.40	43.65
CV (%)	32.83	26.84
AUC_{0-t} (ng.h/mL)		
N	29	30
Geometric mean	1566	1441
CV (%)	33.41	27.93
t_{max} (h)		
Median	3.00	4.00
Minimum	1.00	1.00
Maximum	24.00	24.00

AUC_{0-t}, area under plasma concentration time curve from zero to the time of the last quantifiable concentration
Cmax, maximum plasma concentration
CV, coefficient of variation
N, number of volunteer
t_{max}, time to Cmax

Summary of pharmacokinetic results
The plasma pharmacokinetics of R-bicalutamide following a single oral dose of either a 50 mg marketed tablet (CASODEX) or 2 x 25 mg dispersible tablets was assessed in healthy adult male volunteers. The confidence intervals of treatment ratios for both parameters are comparable and lie well within 0.8 – 1.25, thus the exposure of the two formulations can be considered to be similar.

Summary of safety results
There were no deaths, serious adverse events (SAEs), discontinuations due to AEs, or other significant adverse events (OAEs) reported during this study. There were no clinically significant findings related to clinical laboratory evaluations, vital signs, ECG or physical observations.

Conclusions
Bicalutamide exposure following a single oral dose of either a 50 mg marketed tablet (CASODEX) or 2 x 25 mg dispersible tablets can be considered to be similar on the basis of comparison of R-bicalutamide AUC and C_{max} in healthy adult volunteers. There were no new safety issues identified during this study and both the study drugs are well tolerated.

4.2.2 Clinical Study D6873C00002

Title: An Open-label, Randomised, Single-centre, Cross-over, Phase I Study to Determine the Relative Bioavailability of Anastrozole 1 mg When Administered Orally as Dispersible Tablet and Marketed Tablet (ARIMIDEX™) in Healthy Male Volunteers.

Investigator and Study Center(s)

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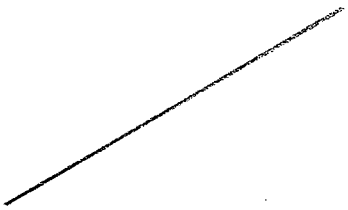
Cheshire, SK10 4TG

STUDY SPONSOR:

AstraZeneca
Alderley Park
Macclesfield
Cheshire, SK10 4TG, UK

BIOANALYTICAL ANALYSIS:

Analysis of pharmacokinetic samples



b(4)

STUDY PERIOD: 02 September 2004 (First volunteer enrolled) – 10 November 2004 (Last volunteer completed)

Objective:
The primary objective of the study was to determine the relative bioavailability of anastrozole when administered as a dispersible oral 1 mg tablet compared with the marketed oral 1 mg tablet (ARIMIDEX) in healthy adult male volunteers

The secondary objectives of the study were:

- To characterize and compare the pharmacokinetics of anastrozole 1 mg, when administered as dispersible oral 1 mg tablet and marketed oral 1 mg tablet (ARIMIDEX) in healthy adult male volunteers.

- To ensure the safety of volunteers, and their tolerability to anastrozole.

Study Design:
This study was a single centre, randomised, open-label, two-period cross-over study in 28 healthy adult male volunteers. The study consisted of two treatment periods (Periods I and II). Each volunteer received two single oral doses of anastrozole (one in each Period). In Period I volunteers were randomised to receive a single oral dose of either

- 1 mg marketed anastrozole tablet (ARIMIDEX), or
- 1 mg dispersible anastrozole tablets

In Period II volunteers crossed over to receive the formulation not received in Period I. Volunteers were kept in the Clinical Pharmacology Unit (CPU) from the evening before each dose of anastrozole until at least 24 hours following dosing. The dose was taken at the same approximate time in both periods. In each Period, samples for PK analysis were collected over a 10 day interval. There was a minimum 21-day washout period between doses. Each volunteer returned for a post-study medical examination within the 14 days following the last PK sample in Period II. For each subject, 16 blood samples were withdrawn for the assessment of anastrozole concentrations in plasma over a 10-day period.

Study Population:
Twenty eight healthy adult male volunteers were enrolled in this study. The mean age was 38.9 years (range 19 to 57 years), mean height was 177.4 cm (range 156 to 189 cm) and mean weight was 80.79 kg (range 60.0 to 107.0 kg). The body mass index for the study population was 25.68 (range 19.3 to 30.0). All volunteers completed the study. All 28 volunteers were non-smokers at entry to the study.

Bioanalytical Analysis:
Quantitative assessment of anastrozole concentration in human plasma was done employing a validated HPLC-MS/MS method. Samples were extracted using a liquid-liquid extraction procedure. Extracted samples were evaporated to dryness and reconstituted and analyzed by HPLC with an AB/MDS Sciex API 4000 mass spectrometer. The calibration curves were analysed at anastrozole concentrations of 0.1, 0.250, 1.0, 2.5, 10.0, 25, 50, 60 ng/mL. The lower limit of quantification (LOQ) for anastrozole was 0.1 ng/mL. Between-batch precision (%CV) results for QC samples

prepared at low, medium, and high QC concentrations of anastrozole was less than or equal to 11.0 % and accuracy (%Bias) ranged from -1.0 to -0.4 %. Between-batch precision (%CV) results of the calibration standards of anastrozole were less than 4 % and accuracy (%Bias) ranged from -0.8 to 1.0 %.

Data Analysis:
PK analysis anastrozole plasma concentration data was performed by non-compartmental analysis. The relative bioavailability of the dispersible tablet in each individual volunteer was determined from the ratios of the AUC and C_{max} of anastrozole obtained following dosing of the dispersible tablet to the AUC and C_{max} of anastrozole obtained following dosing of the marketed tablet. ANOVA was used to compare the log transformed AUC and C_{max} between the dispersible tablet and marketed tablet. The results were presented in terms of the geometric least square means (glsmeans) for each formulation, the relative bioavailability (i.e. the ratios of glsmeans of dispersible 1 mg tablets versus marketed 1 mg tablet), and the associated 90% confidence intervals. Secondary PK parameter were calculated wherever the data allowed. The following secondary pharmacokinetic (PK) variables for anastrozole were determined: Time to reach the maximum plasma concentration (t_{max}), area under plasma concentration-time curve from zero to time t (AUC_{0-t}), terminal rate constant (λz), terminal half-life ($t_{1/2}$), total apparent drug clearance (CL/F), and volume of distribution at steady state (V_{ss}/F).

Pharmacokinetics Results:
Plasma concentrations of anastrozole were comparable after administration of the marketed and dispersible tablets to fasted volunteers. The relative bioavailability, as assessed by the ratios of the dispersible tablet to the marketed tablet was 0.98 (90% CI: 0.96 – 1.01) from comparison of AUC and 0.98 (90% CI: 0.94 – 1.02) from comparison of C_{max}. Thus the exposure of the two formulations can be considered to be similar.

There were four protocol deviations where patient took concomitant medication during the course of study. However, none of the subject took any medications between 72 hours before dosing and 24 hours after dosing. Although all subjects were included in the analysis, a separate analysis was also carried out according to the protocol. No marked difference in parameters values between the two analyses was observed.

Sponsor's PK analyses for secondary parameters of anastrozole were similar for both formulations with T_{max} ranging from 0.5-4.0 hours, $t_{1/2}$ ranging from 30-70 hours

Table 1: Primary PK parameters of Anastrozole

Variable	1 mg marketed tablet	1 mg dispersible tablet
AUC (ng.h/mL)		
N	28	28
Geometric mean	648.9	638.3
CV (%)	19.73	19.17
C_{max} (ng/mL)		
N	28	28
Geometric mean	12.46	12.15
CV (%)	17.41	17.41

AUC = Area under the plasma concentration-time curve from zero to infinity
C_{max} = Maximum plasma concentration
CV= Coefficient of variation
N = Number of volunteers

Table 2: Statistical comparison of primary pharmacokinetics parameters for Anastrozole after oral administration of marketed 1 mg ARIMIDEX tablet and 1 mg dispersible tablet

Variable	1 mg dispersible tablet glsmean[a] (N = 28)	1 mg marketed tablet glsmean[a] (N =28)	Relative bioavailability	90% CI lower limit	90% CI upper limit
AUC (ng.h/mL)	638.35	648.87	0.984	0.962	1.006
C_{max} (ng/mL)	12.15	12.46	0.975	0.935	1.017

[a] Geometric least squares mean
CI = confidence interval

Table 3: Secondary PK parameters for Anastrozole

Variable	1 mg marketed tablet	1 mg dispersible tablet
t_{max} (h)		
Median	1.000	1.000
Minimum	0.500	0.500
Maximum	4.00	4.00
AUC_{0-t} (ng.h/mL)		
N	28	28
Geometric mean	620.2	610.3
CV (%)	18.02	17.03
$t_{½}$ (h)		
N	28	28
Mean	46.44	46.99
SD	9.62	9.77
CL/F (L/h)		
N	28	28
Mean	1.57	1.59
SD	0.3071	0.3016
V_{z}/F (L)		
N	28	28
Mean	97.16	99.53
SD	12.34	13.59

AUC_{0-t} = Area under plasma concentration time curve from zero to the time of the last quantifiable concentration
CL/F = Plasma clearance following oral dosing
CV= Coefficient of variation
N = Number of volunteers
t_{max} = Time to Cmax
$t_{½}$ = Elimination half-life
V_{z}/F = Volume of distribution at steady state following oral dosing

Summary of pharmacokinetic results

The plasma pharmacokinetics of anastrozole following a single oral dose of either a 1 mg marketed tablet (ARIMIDEX) or 1 mg dispersible tablets was assessed in healthy adult male volunteers. The confidence intervals of treatment ratios for both parameters are comparable and lie well within 0.8 – 1.25, thus the exposure of the two formulations can be considered to be similar.

Summary of safety results
There were no deaths, serious adverse events (SAEs), discontinuations due to AEs, or other significant adverse events (OAEs) reported during this study. There were no clinically significant findings related to clinical laboratory evaluations, vital signs, ECG or physical observations.

Conclusions
Anastrozole exposure following a single oral dose of either a 1 mg marketed tablet (ARIMIDEX) or 1 mg dispersible tablets can be considered to be similar on the basis of comparison of anastrozole AUC and C_{max} in healthy adult volunteers. There were no new safety issues identified during this study and both the study drugs are well tolerated

4.2.3 Clinical Study D6873C000047

Title: An Open-label Non-comparative, Multi-centre Study To Assess The Efficacy And Safety Of Bicalutamide When Used In Combination With Anastrozole For The Treatment Of Gonadotropin-independent Precocious Puberty In Boys With Testotoxicosis ((BATT – bicalutamide anastrozole treatment for testotoxicosis)

Investigator and Study Center(s)

Patients were enrolled at 14 centres in 6 countries but were allocated to treatment in only 9 centres in 3 countries as follows: India (2 centres), United Kingdom (1 centre) and United States (6 centres). Two patients who were allocated treatment transferred from one US centre to a new US centre during the study and so patients were treated at 10 centres in total.

STUDY SPONSOR:

AstraZeneca
Alderley Park
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Cheshire, SK10 4TG, UK

BIOANALYTICAL ANALYSIS:

Analysis of pharmacokinetic samples
AstraZeneca
Alderley Park
Macclesfield
Cheshire, SK10 4TG, UK

STUDY PERIOD: 02 September 2004 (First volunteer enrolled) – 10 November 2004 (Last volunteer completed)

Objective:
The primary objective of this study was to assess the efficacy of bicalutamide when used in combination with anastrozole in terms of a reduction in growth rate after 12 months treatment of precocious puberty in boys with testotoxicosis.

The secondary objectives of the study were:

1) To investigate the efficacy of bicalutamide when used in combination with anastrozole in terms of:
    - a reduction in growth rate after 6 months treatment
    - a reduction in bone age maturation rate after 6 and 12 months treatment
    - normalization of growth rate
    - increase in predicted adult height (PAH) after 12 months treatment
    - reduction of signs and symptoms of virilization

2) To assess the safety and tolerability of bicalutamide when used in combination with anastrozole in terms of:
    - gynaecomastia and breast pain adverse events (AEs)
    - all other AEs, withdrawals and laboratory data.

3) To assess pharmacokinetic and pharmacodynamic parameters in achieving an optimal dose of study treatment.

Study Population:
A total of 14 male subjects with a diagnosis of testotoxicosis were enrolled in this study. The age of the subject at the time of enrollment ranged from 2 to 9 years. Their growth rates ranged from 4.15 to 18.92 cm/year (-1.99 to 2.97 SD above the normal rate for boys of the same age). Their bone ages of these subjects ranged from 4.77 to 13.63 years and their ratio of bone age to chronological age at baseline ranged from 1.29 to 3.01. The boys average testicular volume ranged from 3 to 11 mL, their pubic hair stages ranged from 1 to 4 on the Tanner scale and their testes and scrotum development had reached Tanner stage 2 to 4. Eight patients had a male relative with a history of early sexual development. Six of the 14 patients had previously been treated for testotoxicosis.

Table 1: Demographics of the enrolled patients.

Demographic characteristic	Number(%) of patients N=14
Age (years)	
n	14
Mean	3.9
SD	1.9
Median	3.5
Minimum	2
Maximum	9
Age group (years)	
n	14
>=2 - <5	9 (64.29)
>=5 - <10	5 (35.71)
Sex n(%)	
n	14
Male	14 (100.00)
Race n(%)	
n	14
Caucasian	12 (85.71)
Black	1 (7.14)
Other	1 (7.14)
Ethnic group n(%)	
n	14
Hispanic/Latino	1 (7.14)
African-American	1 (7.14)
Asian	3 (21.43)
Not Applicable	9 (64.29)

Study Design and Dose Regimen:
This was a multi-centre, open-label, non-comparative, observational phase II study to investigate the efficacy and safety of bicalutamide in combination with anastrozole for the treatment of testotoxicosis (familial male-limited precocious puberty). Patients were to be given study drugs (bicalutamide and anastrozole) daily for 12 months through individual titration to optimal doses of each drug independently and to be followed up at 3 monthly intervals at 3, 6, 9 and 12 months. After 12 months, all study patients (on or off treatment) were to be followed up annually until they attained their final adult height.

Arimidex (anastrozole) and Casodex (bicalutamide) orodispersible tablets were given orally once daily. The dosing of anastrozole and bicalutamide was independently tailored for each patient. Anastrozole and bicalutamide dose revisions were driven by serum estradiol and plasma bicalutamide concentrations, respectively. Doses of each drug were iteratively adjusted until a dose was reached that gave steady-state trough serum estradiol concentrations of <10 pmol/L (2.7 pg/mL) and R-bicalutamide (the active isomer of bicalutamide) trough plasma concentrations within the range 5-15 µg/mL. Anastrozole

dose escalation was stopped once a plasma anastrozole concentration of 350 ng/mL or a daily dose of 8 mg was reached.

Rationale for dose selection: Clinical data in adults with prostrate cancer have shown that CASODEX at a dose of 50 mg daily provides effective androgen receptor blockade as demonstrated by significant falls in prostate specific antigen (PSA) and improvement in clinical outcome occurring with Casodex usage at this dose. The plasma mean plasma concentration of bicalutamide after daily 50 mg single dose administration to adult males was observed to be 10 µg/mL, with a typical range of 5- 15 µg/mL. Since the exposure of 5-15 µg/mL is shown to be effective in having anti-androgenic effect in adults this exposure window was also chosen for pediatric patients with testotoxicosis. The starting dose of Casodex was 12.5 mg, with dose being titrated up to 150 mg based on observed plasma R-bicalutamide concentrations on Day 21 or later.

Boys with testotoxicosis were expected to have elevated serum estradiol concentrations because of the conversion of excess testosterone to estradiol. Dose selection and titration of Arimidex is based on the plasma estradiol concentrations. The plasma oestradiol concentrations were kept below10 pmol/L as this represents the plasma estradiol concentration in boys at early puberty. Although the serum estradiol concentrations were not elevated at enrollment, patients were started on lowest dose of Anastrozole (0.5 mg).

Bioanalytical Analysis: Quantitative assessment of anastrozole and R-bicalutamide concentration in human plasma was done employing a validated HPLC-MS/MS method (KPV015 and KPV059). R-Bicalutamide plasma samples were extracted using a liquid-liquid extraction procedure. Extracted samples were analyzed by chiral HPLC with an AB/MDS Sciex API 4000 mass spectrometer. The calibration curves were analyzed at R-bicalutamide concentrations of 40, 80, 200, 1000, 5000, 9000, 10000 ng/mL. The lower limit of quantification (LOQ) for bicalutamide was 40 ng/mL. Between-batch precision (%CV) results for QC samples prepared at low, medium, and high QC concentrations of R-bicalutamide was between 5.9 to 9.8 % and accuracy ranged from 99.5 % to 101.9 %. A between-batch precision (% CV) result of the calibration standards of R-bicalutamide was between 4.5 to 10.7 % and accuracy ranged from 98.7 to 102%.

Anastrozole plasma samples were extracted using a protein precipitation procedure. Extracted samples were analyzed by HPLC with an AB/MDS Sciex API 4000 mass spectrometer. The calibration curves were analyzed at anastrozole concentrations of 1, 2, 5, 10, 50, 100, 250 and 500 ng/mL. The lower limit of quantification (LOQ) for bicalutamide was 1 ng/mL. Between-batch precision (%CV) results for QC samples prepared at low, medium, and high QC concentrations of anastrozole was between 6.1to 8.6 % and accuracy ranged from 99.1 % to 103.2 %. A between-batch precision (% CV) result of the calibration standards of anastrozole was between 2.7 to 9.4 % and accuracy ranged from 98.1 to 101.5%.

Pharmacokinetic Results: The mean trough plasma concentrations for R-bicalutamide remained in the pre-specified concentration range of 5- 15 µg/mL. For the 13 patients who were stabilised for bicalutamide, (i.e., attained their potential therapeutic dose), 8 patients were on 50 mg, 4 patients on 100 mg, 1 patient on 12.5 mg bicalutamide. The final stabilised dose for anastrozole was 0.5 mg for 10 patients and 1 mg for 3 patients.

Table 1: Summary of plasma concentration of R-bicalutamide (µg/mL) in pediatric patients.

Summary statistic	Day 56	Day 84	Day 112	Day 140	Month 12
N	13	13	13	12	13
Geometric mean	7.01	7.80	8.01	8.11	8.51
CV (%)	34.7	22.1	40.4	28.8	31.7
Median	6.97	7.51	7.39	8.20	8.46
Min	[				] b(4)
Max					

Table 2: Summary of plasma concentration of Anastrozole (ng/mL) in pediatric patients.

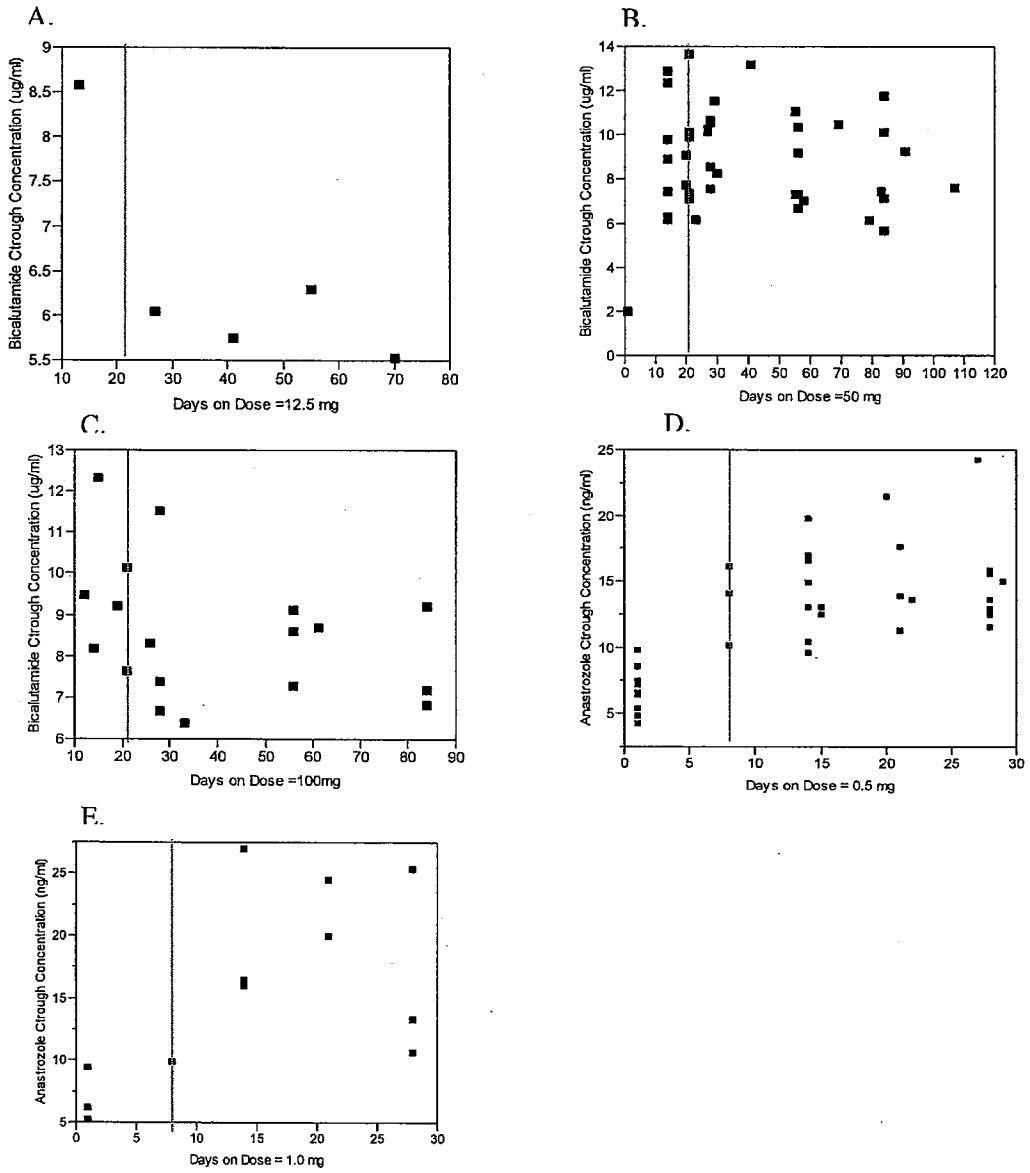
Summary statistic	Day 56	Day 84	Day 112	Day 140	Month 12
N	11	11	11	8	13
Geometric mean	22.13	17.99	15.82	25.70	18.40
CV (%)	68.7	74.5	64.2	75.1	65.7
Median	19.8	15.5	13.6	26.3	13.9
Min	[				] b(4)
Max					

Reviewer's Comments

1) In Adults, once daily dosing of 50 mg Casodex resulted in mean steady state concentration of 8.939 ± 3.5 µg/mL. The steady state C_{trough} plasma concentration in pediatric patients can be considered comparable to the mean steady state plasma concentrations that were observed in adults (Table 1).
2) In Caucasian postmenopausal women, once daily dosing of 1 mg Arimidex resulted in mean steady state trough concentration of 25.7 ng/mL. In pediatric patients the mean steady state C_{trough} plasma concentration was found to be 18.4 ng/mL at Month 12 (Table 2). These differences in trough concentration between adults and pediatric patients can be explained partly because they were targeted to achieve different estradiol concentrations (i.e., <10 pmol/L for pediatric population and <3.7 pmol/L in adults). In addition, in pediatric patient the doses were titrated to keep the estradiol concentration below pre-pubertal estradiol concentration while the adult data came from 1 mg administration.

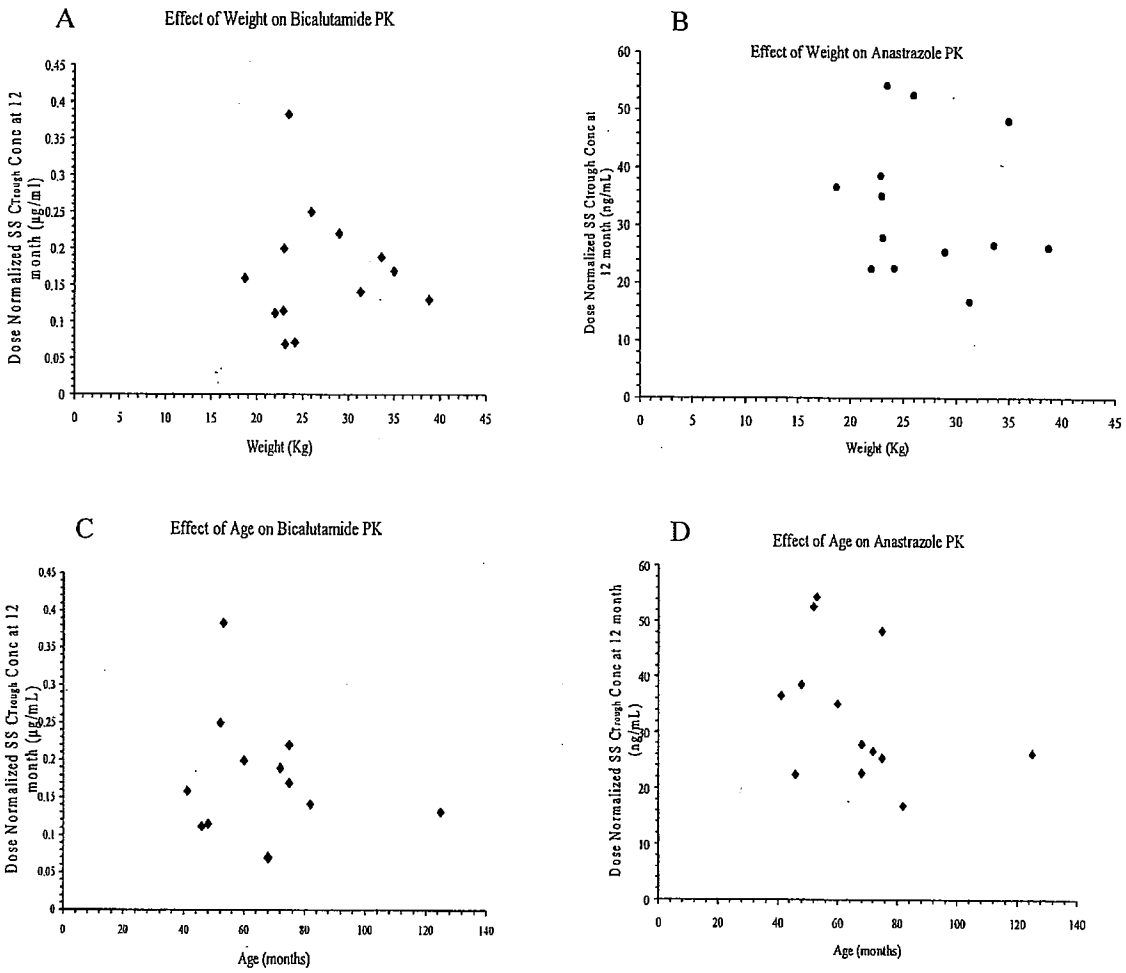
3) The steady-state R-bicalutamide and anastrozole concentrations appeared to be attained in the majority of patients by Day 21 and Day 8, respectively, following once a day dosing (Fig. 1).

Figure 1: Steady State C_{trough} concentration at various doses of bicalutamide, A (12.5 mg), B (50 mg), C (100 mg) and anastrozole D (0.5 mg) and E (1.0 mg). Red line represents Day 21 in figures A, B, C and Day 8 in figures D and E.



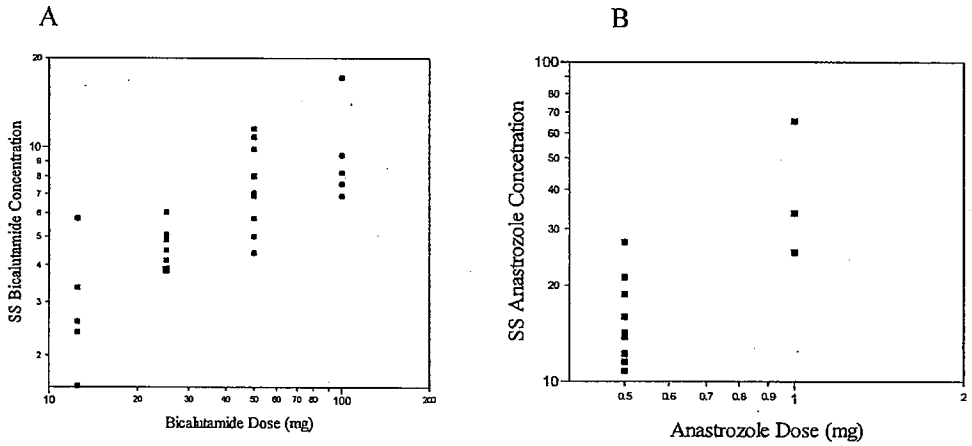
Due to the limited number of sample size no definitive conclusion on the effect of age and body weight on steady state C_{trough} concentrations of bicalutamide and anastrozole can be drawn (Fig. 2). However, in previous review of NDA 22-214 by Dr. Manoj Khurana, it was found that body weight is an important covariate for the determination of clearance and volume of distribution of anastrozole in pediatric patients.

Figure 2: Effect of weight on dose normalized steady state C_{trough} concentration of bicalutamide (A) and anastrozole (B). Effect of age on dose normalized steady state C_{trough} concentration of bicalutamide (C) and anastrozole (D).



Dose Proportionality: Sponsor claims that the [redacted] b(4)

Figure 3: Steady State C_{trough} Concentration of bicalutamide (A) and anastrozole (B) at different doses.



Reviewer's Comment: This reviewer does not agree with the sponsor's claim of [redacted] in their proposed labeling for the following reasons: b(4)

1) Proportional increases of trough plasma concentrations for R-bicalutamide and anastrozole do not add any insight in describing the pharmacokinetic property of the drugs.

2) The number of subjects evaluated at each dose is quite limited and unbalanced. In bicalutamide dose proportionality evaluation there were 5 subjects at 12.5 mg, 7 subjects at 25 mg, 12 subjects at 50 mg and 5 subjects at 100mg. In case of Anastrozole there were only 3 patients on 1mg and 10 patients on 0.5 mg

3) No standard evaluation of the dose-proportionality or dose-linearity of the pharmacokinetics of bicalutamide and anastrozole has been performed in pediatric subjects by the sponsor. When this reviewer performed the dose proportionality evaluation of entire data set available, despite the limited data, dose proportionality was not demonstrated (Table-3).
The power model used for the dose proportionality assessment:
$Log_e(parameter) = a + b*Log_e(dose) + error$ where, a is the intercept and b is the slope.

Table 3: Dose proportionality evaluation of Bicalutamide and Anastrozole

Drug	Parameter	Slope	90%-CI
Bicalutamide	C_{trough}	0.60	0.45-0.75
Anastrozole	C_{trough}	1.73	1.23-2.24

Efficacy Analysis: The primary efficacy variable in this application is change in growth rate (cm/year) after 12 months of treatment with bicalutamide and anastrozole. Efficacy analysis was done by measuring the height of the patients at ≥ 6 months pre-study period, at baseline and after 12 months of treatment. Growth rate at baseline is derived from retrospective data as follows:
GR_B (cm/year) = [height (cm) at baseline – height (cm) at ≥ 6 months pre-study period]/ time interval in years between baseline and pre-study assessment. Change in growth rate after 12 months of the treatment can be obtained by difference in the growth after 12 months (GR_{12} cm/year) and growth rate at baseline (GR_B cm/year).

Several other secondary variables such as rate of change of bone age, bone age to chronological age ratio, normalization of growth rate after 3, 6, 9 and 12 months, change in predicted adult height, change in testicular volume and change in tanner staging were also assessed. Radiographs were used to assess the bone age. Normalization of growth rate was assessed by checking whether the patient's height was within 5^{th} and 95^{th} percentiles compared to the reference population at months 3, 6, 9 and 12 months. Predicted adult height was calculated from the bone age using the Bayley and Pinneau Method. Testicular volume of both testes was measured using either ultrasound or an orchidometer. Development of secondary sexual characteristics was recorded by assigning tanner stages to external genitalia and pubic hair distribution. The number of acne lesions on the face and body was counted by visual inspection and the change in acne lesions and counts were studied at 3, 6 and 12 months. The children's aggression scale - parent version (CAS-P) is a questionnaire designed to assess severity, frequency, pervasiveness and diversity of aggressive, as distinct from nonaggressive, disruptive behaviors. The CAS-P questionnaire was completed at baseline, 3, 6, and 12 months.

Efficacy Results:
The primary efficacy endpoint of this study was to assess the efficacy of bicalutamide when used in combination with anastrozole in terms of the change in the growth rate after 12 months of treatment in boys with testotoxicosis. The clinical efficacy trial failed to meet the primary efficacy endpoint. Please see the review by the medical officer, Dr. Dragos Roman for details.

No exposure response relationship can be drawn from this study.

Reviewer's **Comment:**

1) Exposure-response or dose-response relationship can not be drawn in this study because of the fact that the number of subject evaluated in this study was very limited to make any meaningful interpretation.

2) This study failed to show a statistically significant change in growth rate at 12 months. However, there are some trends suggesting that the effects are greater for the patients with higher growth rate at baseline. Since the number of subjects in, this study was small, this phenomenon can not be ascertained with confidence.

3) There are also some indications that the patients who are previously treated for testotoxicosis showed a lesser effect as compared to patients who do not receive any therapy before. Due to limited sample size, this phenomenon can not be confirmed.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 61,238
NDA 20-498

WRITTEN REQUEST
Amendment # 6

AstraZeneca Pharmaceuticals, LP
Attention: E. Jane Valas, Ph.D.
Associate Director, Regulatory Affairs
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

Dear Dr. Valas:

Please refer to your correspondence, dated March 4, 2008, to IND 61,238 requesting a change to FDA's February 7, 2008, Written Request (WR) Amendment # 5 for pediatric studies for Casodex (bicalutamide) in the treatment of gonadotropin-independent precocious puberty in boys with testotoxicosis.

We have reviewed your proposed change (deletion of the penultimate paragraph in the Written Request Amendment #5 letter) and are granting the requested change. For convenience, the full text of the amended Written Request follows. All other terms stated in our Written Request dated April 17, 2003, as revised February 13, May 7, and October 1, 2004, April 8, 2005, and February 7, 2008, remain the same. For ease of reference, a complete copy of the Written Request follows.

Type of studies:

Study 1. A relative bioavailability (BA) study between a pediatric bicalutamide oral liquid or dispersible tablet formulation (to be developed) and the marketed 50-mg bicalutamide oral tablet.

Study 2. A relative BA study between a pediatric anastrozole oral liquid or dispersible tablet formulation (to be developed) and the marketed 1-mg anastrozole oral tablet.

Study 3. An efficacy study of bicalutamide and anastrozole.

Objectives/ rationale:

Study 1. To investigate the relative BA of bicalutamide between a pediatric liquid or dispersible tablet formulation and the marketed tablet in adults.

Study 2. To investigate the relative BA of anastrozole between a pediatric liquid or dispersible tablet formulation and the marketed tablet in adults.

Study 3. To assess the efficacy and safety of bicalutamide when used in combination with anastrozole for the treatment of precocious puberty in boys with testotoxicosis.

Indication to be studied:

Treatment of gonadotropin-independent precocious puberty in boys with testotoxicosis.

Study design:

Study 1. This is a randomized, open-label, crossover study in healthy adult volunteers who will receive orally 50 mg bicalutamide in either liquid/dispersible tablet or tablet form in the first treatment period. After a washout period of at least 63 days, the subjects will receive 50 mg bicalutamide in either liquid/dispersible tablet or tablet form, whichever they did not receive during the first treatment period. Serial blood samples will be collected at specified times after each treatment to measure plasma bicalutamide concentrations. This study may be conducted at the same time as, but should not be after, the proposed pediatric clinical safety and efficacy study.

Study 2. This is a randomized, open-label, crossover study in healthy adult volunteers who will receive orally 1 mg anastrozole in either liquid/dispersible tablet or tablet form in the first treatment period. After a washout period of at least 20 days, the subjects will receive 1 mg anastrozole in either liquid/dispersible tablet or tablet form, whichever they did not receive during the first treatment period. Serial blood samples will be collected at specified times after each treatment to measure plasma anastrozole concentrations. This study may be conducted at the same time as, but should not be after, the proposed pediatric clinical safety and efficacy study.

Study 3. A 12-month, open-label, multicenter, observational study of bicalutamide used in combination with anastrozole in boys with testotoxicosis. The study will have at least 12 protocol-defined completers with a full complement of protocol-defined efficacy and safety data. A minimum of 5 patients must be treatment-naïve and the remaining patients may be treatment-experienced to antiandrogen therapy. The occurrence of central precocious puberty (CPP) will be monitored and will include a GnRH stimulation test at regular intervals or at any point where the investigator believes CPP has occurred. If CPP develops, treatment with a GnRH agonist must be initiated. During the study, periodic drug level monitoring for both bicalutamide and anastrozole will be performed. To this end, determine plasma levels for both drugs at the following timepoints: predose, trough drug concentrations before the second dose, between days 8 and 14, and at 1 month, 2 months, and 3 months after the first dose. The determination of plasma drug concentrations should allow quick turnaround time for dose adjustment purposes. Every dose adjustment should be followed by trough plasma drug level measurements between days 8 and 14, and at 21 days, 1 month, 2 months, and 3 months after the dose change. Dose adjustment should be based on trough plasma drug concentrations achieved no sooner than three drug half-lives after the previous dose. An assessment of the dose and dosing schedule for both drugs will be performed after evaluating the pharmacokinetic information for the first four patients on treatment. This process will be repeated for additional panels of four patients until an appropriate dose regimen is established.

Age group and number of subjects to be studied:

Studies 1 and 2. Adult volunteers, with 24 volunteers completing each study.

Study 3. Boys – 2 years of age and older, with 12 protocol-defined completers who have a full complement of protocol-defined efficacy and safety data at the end of one year of treatment.

Entry criteria:

Studies 1 and 2. Healthy, adult, non-smoking volunteers who do not receive any prescription or over-the-counter medications (except limited use of acetaminophen as an analgesic) or any dietary supplements.

Study 3. Diagnosis of testotoxicosis made by clinical plus biochemical criteria; no evidence of central precocious puberty as demonstrated by GnRH stimulation test. A minimum of six months of pre-study growth information (height and height velocity, will be available prior to enrollment. In addition, bone age radiographs must be available at screening/baseline for calculation of bone age/chronological age ratio in all patients. If, in addition, six months of pre-study bone age information are available, the baseline rate of bone age maturation should be calculated. Collection of pre-study growth data must meet strict endocrinological standards of accuracy and should be well documented.

Endpoints:

Studies 1 and 2. Bicalutamide and anastrozole pharmacokinetic parameters, such as relative BA, $AUC_{0-\infty}$, AUC_{0-t}, CL/ F, V_d/ F, C_{max}, T_{max}, λ_z, $t_{1/2}$, and their descriptive statistics should be evaluated.

Study 3. Primary endpoint: change in growth rate after 12 months of treatment relative to the growth rate during the ≥ 6-month pre-study period for treatment-naïve patients.

Additional assessments for treatment-naïve patients:

Study 3.

- Change in growth rate (centimeters and standard deviation score) after 6 months of treatment relative to the growth rate during the ≥ 6-month pre-study period
- Bone age/chronological age ratio after 6 and 12 months of treatment relative to the bone age/chronological age ratio at baseline
- Change in rate of bone age maturation after 6 and 12 months of treatment relative to the rate of bone age maturation during the ≥ 6-month pre-study period for patients with baseline rate of bone age maturation information available (rate of bone age maturation will be defined as interval change in bone age/interval change in chronological age)
- Comparison of on-study data with historical data from the referenced study (Lescheck et al.) at the end of one year of treatment for growth rate, bone age maturation (if pre-study

data are available), and percentage of patients showing improvement in aggressive behavior and acne lesions

- Number and percent of patients who achieve and/or maintain growth rates between the 5th and the 95th percentile
- Change in predicted adult height (PAH) at the end of the study compared to baseline PAH
- Incidence of patients with breast pain and gynecomastia at the beginning and the end of the trial
- Evolution of signs and symptoms of virilization while on study medication (virilization signs and symptoms to be followed are: testicular volume, Tanner staging, number of acne lesions, and aggressive behavior)
- Descriptive statistics of the plasma bicalutamide and anastrozole concentrations.

For non-naïve patients the same assessments described for treatment-naïve patients will be conducted.

Drug information:

Studies 1 and 2.

Dose:	50 mg bicalutamide or 1 mg anastrozole
Dosage form:	liquid or dispersible tablet (to-be-developed for both test medications), or marketed tablet (for both marketed test medications)
Route of administration:	oral
Regimen:	each subject will receive the liquid or dispersible tablet or marketed tablet for both test medications
Formulation:	pediatric liquid or dispersible tablet (to-be-developed for both test medications), or marketed tablet (for both marketed test medications)

Study 3.

Dosage form:	liquid or dispersible tablet (to-be-developed)
Route of administration:	oral
Regimen:	bicalutamide will be started at a daily dose of 0.5 to 1 mg/kg and will be titrated to a plasma level in a range of 5 to 15 µg/mL; anastrozole will be started at a daily dose of 0.5 mg and will be titrated with the goal of maintaining normal serum estrogen levels
Formulation:	age appropriate

Use an age-appropriate formulation in the studies described above. Any unapproved formulation will need to be supported by a study of relative bioavailability; these studies may be conducted in adults. A formulation you develop for use in children should meet standards for marketing approval. If you cannot develop a potentially marketable

formulation, you will need to document the attempt to do so, and the Agency will consider another formulation that is standardized and palatable. Full study reports of any relative bioavailability studies should be submitted to the Agency as part of the response to this Written Request.

Drug-specific safety concerns:

The safety profile of bicalutamide/anastrozole combination in children is not known. To this end, a 3- month juvenile rat toxicity study (males only) of bicalutamide/anastrozole combination will be completed and the results will be presented to the agency for review prior to initiating the clinical study.

During the clinical study, bicalutamide-specific adverse events should be monitored, particularly, hepatic adverse events (e.g., elevated transaminases, jaundice, diarrhea, nausea, vomiting, asthenia). Anastrozole-specific adverse events identified in the drug label should also be monitored.

Statistical information:

For treatment-naïve patients:

- Change in growth rate after 12 months of treatment relative to growth at baseline will be analyzed using a one-sample T-test. A 95% 2-sided confidence interval also will be calculated for the mean change in growth rate. All other endpoints will be summarized using descriptive statistics. Mean changes and individual changes will be presented.

- Change in growth rate and, if pre-study data are available, change in rate of bone maturation after 12 months of treatment will be compared with the data generated in the referenced study (Lescheck, et al.).

For non-naïve patients, the efficacy data will be summarized descriptively.

Labeling that may result from the studies:

Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of reports to be submitted:

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

Although not required at the time of pediatric exclusivity determination, we request that you monitor the study participants until final height is reached in all patients. To this end, submit the information in annual reports. Patients should be monitored with respect to above listed endpoints/assessments every 6 to 12 months.

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before June 30, 2008. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request:

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request, you must notify the Agency as to your intention to act on the Written Request. If you agree to the request, then you must indicate when the pediatric studies will be initiated.

Reports of the studies that meet the terms of the Written Request dated February 7, 2008, as amended by this letter must be submitted to the Agency on or before June 30, 2008, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit protocols for the above studies to **IND 61,238** and clearly mark your submission, **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a new drug application (NDA) with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e., approval, approvable, not approvable); or
4. the exclusivity determination (i.e., granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to **IND 61,238.** Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval), 2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice in accordance with section 505A(e)(2).

Under section 505A(j) of the Act, regardless of whether the studies demonstrate that bicalutamide is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the studies.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e., complete or partial response);
2. the status of the application (i.e., withdrawn after the supplement has been filed or pending);
3. the action taken (i.e., approval, approvable, not approvable); or
4. the exclusivity determination (i.e., granted or denied).

Finally, please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and

submission of trial results. Additional information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov

If you have any questions, please call Jennifer Johnson, Regulatory Project Manager, Division of Metabolism and Endocrinology Products, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Acting Director
Office of Drug Evaluation II
Center for Drug Evaluation Research

Linked Applications	Sponsor Name	Drug Name
IND 61238	ASTRAZENECA PHARMACEUTICALS LP	CASODEX(BICALUTAMIDE)ORALLY DISINTEGRATG

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/s/

CURTIS J ROSEBRAUGH
05/09/2008

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

/s/

Ritesh Jain
12/15/2008 01:11:44 PM
BIOPHARMACEUTICS

Sally Choe
12/15/2008 01:23:50 PM
BIOPHARMACEUTICS

DFS 8/15/08

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA Number	22-310	Brand Name	Casodex
OCP Division (I, II, III, IV, V)	DCP II	Generic Name	Bicalutamide oral tablet
Medical Division	DMEP	Drug Class	
OCP Reviewer	Lucun Bi, Ph.D.	Indication(s)	In combination with Arimidex (anastrozole) for young boys with testotoxicosis
OCP Pharmacometric Reviewer	N/A	Dosage Form	Oral tablet
OCPB Team Leader	Sally Choe, Ph.D.	Dosing Regimen	
Date of Submission	June 25, 2008	Route of Administration	Oral administration
Estimated Due Date of OCP Review	November 15, 2008	Sponsor	AstraZeneca
PDUFA Due Date	December 25, 2008	Priority Classification	Priority
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				

In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	X	1	1	d6873c00047
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	2	2	d6873c00002 and d6873c00003. Both are single dose crossover relative bioavailability study.
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		3	3	

Filability

	"X" if yes	Comments
Application filable?	X	**Comments to the Sponsor: Need bioanalytical method validation reports for bicalutamide and anastrozole from both —— and AstraZeneca; plasma sample analysis reports for bicalutamide and anastrozole for study d6873c00047; method validation for serum estradiol and serum estradiol sample analysis report for study d6873c00047.**
Submission in Brief: See the details below.	**Reviewer's Comments:**	**Clinical Pharmacology Review will focus on the 3 clinical studies and the proposed labeling. DSI inspection will not be requested.**

b(4)

Submission in Brief:

The sponsor, AstraZeneca Pharmaceuticals LP (AstraZeneca), submitted a type 6 NDA (NDA22-310) providing safety, efficacy, and pharmacokinetic (PK) information on the use of bicalutamide (Casodex®, NDA20-498), in combination with anastrozole (Arimidex®, NDA20-541) as oral dispersible tablet for the treatment of testotoxicosis in male pubertal patients.

Testotoxicosis is a rare disease observed in young boys, who begin pubertal development by 2 to 3 years of age. Bicalutamide, an oral non-steroidal androgen inhibitor, blocks the androgen-induced growth, and minimize the stimulation effect by testosterone and dihydrotestosterone. Anastrozole is a non-steroidal selective inhibitor of the aromatase enzyme that inhibits the production of estrogens from testosterone. The combination of bicalutamide and anastrozole could reduce the androgen- and estrogen-induced growth and allow uninterrupted pubertal development in these patients with testotoxicosis.

This NDA is being filed in order to obtain Pediatric Exclusivity for bicalutamide based on three clinical studies specified in the Pediatric Written Request from FDA. The three clinical studies submitted in this NDA are as follow:

- The relative bioavailability of bicalutamide 50 mg when administered as dispersible tablet and marketed tablet (CASODEX™) in healthy male volunteers (Study D6873C00003; referred hereafter as Study 0003 [FDA Written Request reference "Study 1"]).
- The relative bioavailability of anastrozole 1 mg when administered orally as dispersible tablet and marketed tablet (ARIMIDEX™) in healthy male volunteers (Study D6873C00002; referred hereafter as Study 0002 [FDA Written Request reference "Study 2"]).
- A 12-month, open-label, multicenter, observational study of bicalutamide used in combination with anastrozole in boys with testotoxicosis (Study D6873C00047; referred hereafter as Study 0047 [FDA Written Request reference "Study 3"]).

The first two are relative bioavailability studies, which demonstrate the dispersible formulation tablets are bioequivalent to the marketed products. The two relative bioavailability studies allow the sponsor to bridge the dispersible tablets that were used in efficacy trial (D6873C00047) to the approved drug formulations. The sponsor also submitted a 90 day toxicology study, which assessed the effect of the combination of bicalutamide and anastrozole on the fertility of juvenile male rat following 90 day daily administration (Study 0514GR).

The sponsor conducted the third clinical study (Study 0047) administering bicalutamide and anastrozole to treat young boys with testotoxicosis for 12 month. This study provided the safety and efficacy data of the combination of bicalutamide and anastrozole in pediatric population. In Study 0047, both bicalutamide and anastrozole were dose titrated in the pediatric patients in order to reach the optimal plasma concentration. The dosing records and plasma concentration of both drugs were found in SAS transport files (Module 5).

Even though the orodispersible bicalutamide tablets was used in the efficacy study, the sponsor stated that this formulation as a long term approach was not appropriate, and oral suspension will

be used for the treatment for the pediatric patients. The stability test of the oral suspension was submitted in Module 3.

The sponsor has presented the clinical summary of efficacy (CSE) and clinical summary of safety data (CSS) in the Clinical Summary (Module 2.7). The three clinical study reports are in Module 5.

Bioanalytical method validation for the determination of bicalutamide and anastrozole in plasma were not attached in the submission. Bioanalytical sample analysis reports for all three studies were submitted.

The sponsor also submitted an annotated label for bicalutamide.

Study 0003: The relative bioavailability of bicalutamide 50 mg when administered as dispersible tablet and marketed tablet (CASODEX™) in healthy male volunteers (Study D6873C00003)

Study objectives:

The primary objective of the study was to determine the relative bioavailability of bicalutamide when administered as a dispersible oral 2×25 mg tablets compared with marketed oral 25 mg marketed tablet (CASODEX™) in healthy male volunteers.

The secondary objective is to characterize and compare the pharmacokinetics of bicalutamide 50 mg; and to ensure the safety of volunteers and their tolerability to bicalutamide

Study Design:

This is a randomized, open-label, single-center, cross-over study in healthy adult male adults. The study had two periods:

In period 1, volunteers were randomized to receive one the following treatments.

- 2×25 mg dispersible bicalutamide tablets, or
- 50 mg marketed tablet (CASODEX™).

In period 2, volunteers crossed over to receive the alternate treatment.

50 mg dose was used in this study. The oral tablet(s) was taken with 240 mL purified water. Washout period was at least 63 days between the two doses.

Serial blood sample were collected at predose, 0.25, 0.5, 1, 2, 3, 5, 9, 12, 15, 24, 36, 48, 72, 168, 336, 504, 672, and 840 hours pose dose for the measurement of plasma bicalutamide concentration after each treatment.

Study Results:

Analytical Details:

The analysis of plasma bicalutamide was conducted by [ ] applying a validated LC/MS/MS method. The — facility is located at [ ]

b(4)

Pharmacokinetics:

Plasma AUC and Cmax of the R-bicalutamide (which is the active enantimer) for the dispersible oral tablet were compared to that of CASODEX. In addition, $AUC_{(0-t)}$, CL/F, Vss/F, Tmax, λz and $t_{1/2}$ following administration with the dispersible oral tablet or CASODEX were also obtained.

Statistical analysis:

The geometric and arithmetic means of AUC_{inf} and C_{max} for the test product (dispersible bicalutamide, 2×25 mg tablet) and reference product (marketed bicalutamide 50 mg) were determined, and the 90% confidence interval boundary for non statistical significance was set at 80% to 125% for bicalutamide.

Table 2 **Comparison of AUC and C_{max} of R-bicalutamide for the CASODEX 50 mg commercial tablet and 2 x 25 mg orodispersible tablets**

Variable	Orodispersible tablet[a] 2 x 25 mg (glsmean)	Commercial tablet[b] 50 mg (glsmean)	Relative bioavailability	90% CI lower limit	90% CI upper limit
AUC (ng.h/ml)	187957 (n=29)	202893 (n=27)	0.93	0.89	0.96
Cmax (ng/ml)	793 (n=30)	863 (n=29)	0.92	0.90	0.94

[a] Refer to IND 61,238 for composition.
[b] Refer to NDA 20-498 for composition.
AUC Area under the plasma concentration time curve from zero to infinity.
CI Confidence interval.
C_{max} Maximum plasma concentration.
glsmean Geometric least squares mean.

Study 0002 An open-label, Randomized, Single-center, cross-over, phase 1 study to determine the relative bioavailability of anastrozole 1 mg when administered orally as dispersible tablet and marketed tablet (ARIMIDEX™) in healthy male volunteers.

Study objectives:

The primary objective of the study was to determine the relative bioavailability of anastrozole when administered as a dispersible oral 1 mg tablet compared with marketed oral 1 mg (ARIMIDEX™) in healthy adult male volunteers.

The secondary objective is to characterize and compare the pharmacokinetics of anastrozole 1 mg and marketed oral 1 mg (ARIMIDEX™); and to ensure the safety of volunteers and their tolerability to anastrozole.

Study Design:

This is a randomized, open-label, crossover study in healthy adult male volunteers. The study had two periods:

In period 1, volunteers were randomized and received wither

- 1 mg marketed tablet ARIMIDEX or
- 1 mg dispersible tablet anastrozole

In period 2, volunteers crossed over to receive the alternate treatment.

1 mg anastrozole is used in this study. The oral tablet(s) was taken with 240 mL purified water. Washout period was at least 21 days between the two doses.

Serial blood sample were collected at predose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 72, 96, 120, 144, 168, and 216 hours post dose for the measurement of plasma anastrozole concentration after each treatment.

Study Results:

Analytical Details:

Concentration of anastrozole in plasma samples was determined by [redacted] applying a validated LC/MS/MS method. The [redacted] facility is located at [redacted] b(4)

Pharmacokinetics:

Non-compartmental analysis was applied to estimate the PK parameters. Plasma AUC and Cmax of the anastrozole for the dispersible oral tablet were compared to that of Arimidex. In addition, $AUC_{(0-t)}$, CL/F, Vss/F, Tmax, λz and $t_{1/2}$ following administration with the dispersible oral tablet or ARIMIDEX were also obtained.

Statistical analysis:

AUC and Cmax was log transformed and then analyzed by mixed effect analysis of variance (ANOVA). The geometric and arithmetic means of AUC_{inf} and C_{max} for the test product (dispersible anastrozole, 1 mg tablet) and reference product (marketed bicalutamide, ARIMIDEX 1 mg) were determined, and the 90% confidence interval boundary for non statistical significance was set at 80% to 125% for anastrozole.

Table 2 **Comparison of AUC and C_{max} of commercial ARIMIDEX 1 mg tablet and orodispersible tablet**

Variable	1 mg orodispersible tablet[a] (glsmean)	1 mg commercial tablet[b] (glsmean)	Relative bioavailability	90 % CI lower limit	90 % CI upper limit
AUC (ng.h/mL)	638	649	0.98	0.96	1.01
C_{max} (ng/mL)	12	12	0.98	0.94	1.02

[a] Tablet batch number P/4061/08, refer to IND 61,238 for composition.
[b] Tablet batch number CD657, refer to NDA 20-541 for composition.
AUC Area under the plasma concentration time curve from zero to infinity.
C_{max} Maximum plasma concentration.
Glsmean Geometric least squares mean.
CI Confidence interval.
Data from study number D6873C00002.
n=28.

Study 0047 An Open-label Non-comparative, Multi-center Study to Assess the Efficacy and Safety of Bicalutamide When Used in Combination with Anastrozole for the Treatment of Gonadotropin-independent Precocious Puberty in Boys with Testotoxicosis.

Study objectives:
The primary study objective is to assess the efficacy and safety of bicalutamide when used in combination with anastrozole for the treatment of precocious puberty in boys with testotoxicosis.

The secondary objectives are to assess the efficacy, safety and tolerability of bicalutamide when used in combination with anastrozole; and to assess the pharmacokinetics and pharmacodynamics in achieving the optimal dose of the treatment.

Study Design:
In this 12-month, open-label, multicenter, observational study, young boys with testotoxicosis pediatric patients will receive bicalutamide in combination with anastrozole. The study drugs were 0.5 mg and 1 mg anastrozole orodispersible tablets and 12.5 mg and 25 mg bicalutamide orodispersible tablets. Each patient received the combination of these drugs orally once daily. Bicalutamide had dose titration so that the final stable concentration for R-bicalutamide was within the range of 5 to 15 µg/mL. Anastrozole dose was titrated in order to suppress the oestradiol in these patients to less than 10 pmol/L (2.7 pg/mL), which is the oestradiol level found in boys during early puberty. During the study, periodic drug level monitoring for both bicalutamide and anastrozole were performed at the specified time points.

Analytical Details:

Concentrations of anastrozole and bicalutamide in plasma samples were determined by AstraZeneca at the test facility located at CPD. Alderley Park, AstraZeneca UK Limited, Alderley Park, Macclesfield, Cheshire, SK10 4TG, UK.

Trough concentrations of bicalutamide were generally remained in the pre-specified range of 5 to 15 µg/mL, which were listed in the following table from Day 56 to Month 12.

Table 31 **Summary of plasma concentrations (µg/mL) of R-bicalutamide: Safety set**

Summary statistic	Day 56	Day 84	Day 112	Day 140	Month 12
N	13	13	13	12	13
Geometric mean	7.01	7.80	8.01	8.11	8.51
CV (%)	34.7	22.1	40.4	28.8	31.7
Median	6.97	7.51	7.39	8.20	8.46
Min	[				
Max					]

b(4)

Patient E0003004 was lost to follow up before Day 56 and so did not provide data for this table. Patient E0003002 did not provide a sample at Day 140.
CV Coefficient of variation
Data derived from Table 11.2.9.1

Trough concentrations of anastrozole ranged from 15.82 to 25.70 ng/mL, which were listed in the following table from Day 56 to Month 12. Because patients started to receive anastrozole 2 weeks earlier and reached stabilization period at different time as compared to bicalutamide, thereby 2 patients did not have trough anastrozole concentration on Days 56, 84, 112, and 5 patients did not Ctrough at Day 140. Summary of trough plasma concentration of anastrozole and serum oestradiol concentration were listed in the two tables below. The sponsor listed graphs showing each individual's anastrozole dose adjustment and the plasma anastrozole concentration in the study report from page 375 to 402. Patients generally had stable anastrozole plasma concentration.

Table 32 Summary of plasma concentrations (ng/mL) of anastrozole: Safety set

Summary statistic	Day 56	Day 84	Day 112	Day 140	Month 12
N	11	11	11	8	13
Geometric mean	22.13	17.99	15.82	25.70	18.40
CV (%)	68.7	74.5	64.2	75.1	65.7
Median	19.8	15.5	13.6	26.3	13.9
Min	[				]
Max					

b(4)

Patient E0003004 was lost to follow up before Day 56 and so did not provide data for this table. At Day 56 and Day 84 no sample was available for Patients E0054003 and E0054004. At Day 112 no sample was available for E0003002 and E0003003. At Day 140 no sample was available for Patients E0002001, E0003002, E0009001, E0054003 and E0054004.

CV Coefficient of variation

Data derived from Table 11.2.9.2

Table 33 Summary of serum oestradiol concentrations (pmol/L): Safety set

Summary statistic	Day 56	Day 84	Day 112	Day 140	Month 12
N	11	11	12	8	13
Mean	9.58	9.45	9.18	9.32	9.32
SD	1.33	0.88	0.00	0.39	0.51
Median	9.18	9.18	9.18	9.18	9.18
Min	[				]
Max					

b(4)

Note that 9.18 pmol/L is the LOQ for the assay.

Data derived from Table 11.3.7.6

Median	19.8	15.5	13.6	26.3	13.9
Min	[				]
Max					

b(4)

Patient E0003004 was lost to follow up before Day 56 and so did not provide data for this table. At Day 56 and Day 84 no sample was available for Patients E0054003 and E0054004. At Day 112 no sample was available for E0003002 and E0003003. At Day 140 no sample was available for Patients E0002001, E0003002, E0009001, E0054003 and E0054004.

CV Coefficient of variation

Data derived from Table 11.2.9.2

Attachment 1: Tabular Listing of Clinical Studies

Table 1 Listing of clinical studies

Type of study	Study	Location of study report	Objectives of the study	Study design and type of control	Test product; dosage regimen; route of administration	Number of subjects	Diagnosis of patients	Duration of treatment	Study status; type of report
Bio-availability	0093	Module 5.3.1.1	Relative bioavailability	Open label crossover	Bicalutamide 50 mg marketed tablet and 2 x 25 mg dispersible tablets; oral	30	Healthy adult male volunteers	Single dose	Complete; Full
Bio-availability	0092	Module 5.3.1.1	Relative bioavailability	Open label crossover	Anastrozole 1 mg marketed tablet and 1 mg dispersible tablet; oral	28	Healthy adult male volunteers	Single dose	Complete; Full
Efficacy	0047	Module 5.3.5.2	Safety and efficacy	Open label	Bicalutamide dispersible tablet, o.d.; oral and anastrozole dispersible tablet, o.d.; oral. Doses tailored for each patient	14 treated	Prepubertal boys with testotoxicosis	12 months	Complete; Full

o.d. Once daily.

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/s/

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8/15/2008 10:20:36 AM
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