CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-310

CHEMISTRY REVIEW(S)

12/11/08

CHEMISTRY REVIEW

NDA 22-310

Casodex® (bicalutamide) Tablets, 50 mg.

Casodex® Oral Suspension, 10 mg/mL.

Arimidex® Oral Suspension, 0.2 mg/mL.

AstraZeneca UK Limited

Chemistry Review

Donald N. Klein, Ph.D.

Branch VII, DPE, ONDQA

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CHEMISTRY NDA REVIEW DATA SHEET

1. **NDA 22-310 Casodex® (bicalutamide) Tablets.**

   Casodex® Oral Suspension.

   Arimidex® Oral Suspension.

2. **CHEM. REVIEW:** # 1.

3. **REVIEW DATE:** December 11, 2008.

4. **REVIEWER:** Donald N. Klein, Ph.D.

5. **PREVIOUS DOCUMENTS:**
   NDA 20-498 *(approved 10/4/1995)*: Casodex® (bicalutamide) Immediate Release Tablet, 50 mg.

   NDA 20-541 *(approved 12/27/1995)*: Arimidex® (anastrozole) Immediate Release Tablet, 1 mg.

   IND 61,238 *(active since 7/14/2004)*: The following respective orodispersible tablets were used in supportive clinical studies:
   Casodex® (bicalutamide) orodispersible tablets, 12.5 mg and 25 mg.

   Arimidex® (anastrozole) orodispersible tablets, 0.5 mg and 1.0 mg.

6. **SUBMISSION BEING REVIEWED:**

Submissions Reviewed	Document Date
Original	25-JUN-2008
CMC Memo to File (PAL)	04-AUG-2008
Microbiology Consult	05-AUG-2008
74 Day Filing Letter	03-SEPT-2008
Microbiology Review	31-OCT-2008
CMC question *(internal)* about draft labeling	14-NOV-2008
CMC question *(internal)* about draft labeling	17-NOV-2008
CMC Information Request *(e-mail)*	19-NOV-2008
Response *via* BC Amendment	25-NOV-2008
Internal review team Meeting	25-NOV-2008
CMC Information Request *(e-mail)*	25-NOV-2008
Response *via* BC Amendment	03-DEC-2008

7. **NAME AND ADDRESS OF APPLICANT:**

AstraZeneca UK Limited
Alderley Park
Macclesfield, Cheshire
SK 10 4TG
England

U.S. Agent:
AstraZeneca Pharmaceuticals LP
Cindy Lancaster, MS, JD
Executive Director, Regulatory Affairs
P.O. Box 8355
Wilmington, DE 19803-8355

8. **DRUG PRODUCT NAME:**
Proprietary: Casodex®.
Nonproprietary/USAN (1994): Bicalutamide.
Code Name/Number: ICI 176,334.

Proprietary: Arimidex®.
Nonproprietary/USAN (1995): Anastrozole.
Code Name/Number: ICI D1033; ZD1033

9. **LEGAL BASIS FOR SUBMISSION:** Pursuant to section 505A of the Food, Drug, and Cosmetic Act, N22-310 is filed in order to obtain Pediatric Exclusivity Determination.

10. **PHARMACOLOGICAL CATEGORY/INDICATION:** Male pubertal patients with testotoxicosis (rare disease).

11. **DOSAGE FORM:**

Casodex®: Oral suspension.

Arimidex®: Oral suspension.

12 **STRENGTH:**

Casodex® oral suspension: 10 mg/mL.

Arimidex® oral suspension: 0.2 mg/mL.

13. **ROUTE OF ADMINISTRATION:**

Casodex® oral suspension: Oral.

Arimidex® oral suspension: Oral.

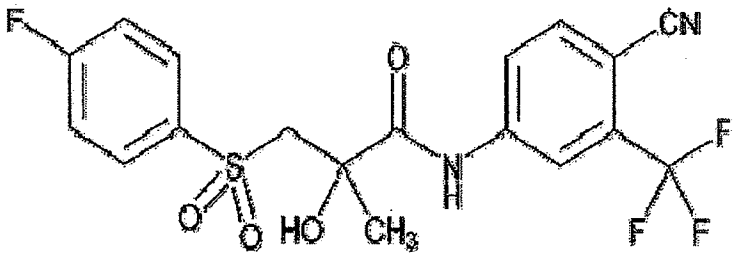
14. **DISPENSED:** x RX __OTC.

15. **SPOTS** (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): ___Yes x No.

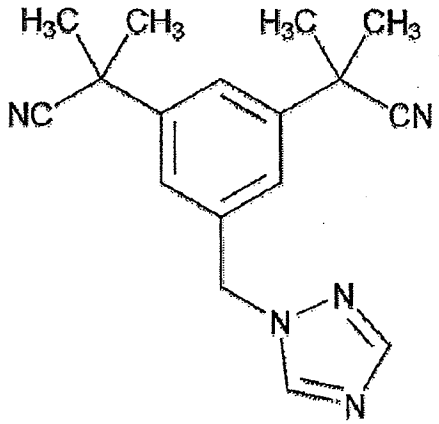
16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:**

Bicalutamide:

Chemical Name: Propanamide, *N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (±)-.
Molecular Formula: $C_{18}H_{14}F_4N_2O_4S$.
MW: 430.37.
CAS: 90357-06-5.
Chemical Structure:



Anastrozole:
Chemical Name: 1,3-Benzenediacetonitrile, α,α,α',α'-tetramethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-.
Molecular Formula: $C_{17}H_{19}N_5$.
MW: 293.37.
CAS: 120511-73-1.
Chemical Structure:



17. RELATED/ SUPPORTING DOCUMENTS:

A. DMF's:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
[				1	Adequate for Microbiology	31-OCT-2008	Reviewed by Dr. Riley
]				1	Adequate for CMC	21-NOV-2008	Reviewed by Dr. Klein

b(4)

[1]Action codes for DMF Table:
1--DMF Reviewed
Other codes indicate why the DMF was not reviewed, as follows:
2--Type 1 DMF
3--Reviewed previously and no revision since last review
4--Sufficient information in application
5--Authority to reference not granted
6--DMF not available
7--Other (explain under "Comments")

[2]Adequate, Inadequate

B. Other Documents:

1. The following oral suspension NDAs (N21-483 and N17-453) had been reviewed by Dr. Klein (HFD-120, HFD-130, and DPE) and the N22-310 Specification and Stability CMC Information Requests (11/18/08 and 11/25/08) were based on these respective, approved NDAs:
   a. **N17-453** Proglycem® (diazoxide, USP) Oral Suspension, SCS-012 and SCS-013 *(approved in 2008)*.
   b. **N21-483** Geodon® (ziprasidone HCl) Oral Suspension *(approved in 2006)*.

18. STATUS:

Reviews	Recommendation	Date	Reviewer
EES	*n/a*	*n/a*	*n/a*
Method Validation	*n/a*	*n/a*	*n/a*
Medical	*Pending*	*Pending*	Dragos Roman, M.D.
Microbiology	Approval	31-OCT-2008	Bryan Riley, Ph.D.
Clinical Pharmacology	*Pending*	*Pending*	Lucun Bi, Ph.D.
Environmental Assessment	Acceptable	11-DEC-2008	Donald Klein, Ph.D.
Pharm/Tox	*Refer to the Pharm/Tox review*	14-NOV-2008	Karen Davis-Bruno, Ph.D.

The Chemistry Executive Summary

I. Recommendations:

A. Recommendations and Conclusions on Approvability.

NDA 22-310 is recommended approval from the CMC standpoint.

B. Recommendations on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

N/A

II. Summary of Chemistry Assessments:

A. Description of Drug Product and Drug Substance

Drug Products

As requested by the Agency the applicant developed the following respective oral suspensions:

Casodex® (bicalutamide) oral suspension, 10 mg/mL.

Arimidex® (anastrozole) oral suspension, 0.2 mg/mL.

In the respective Pharmaceutical Development sections, the applicant discusses the investigation of — formulations each using a different suspending agent — ⌐ ⊥. Consequently, the — produced the most stable suspension. b(4)

In support of the ⌐ ⊥ (commercially available, over-the-counter product) the applicant references **DMF** — Type IV, *(LOA dated 1/9/2008)*. The Microbiology Division was consulted (8/5/08) and Dr. Riley found **DMF** — adequate (10/31/08) for — Subsequently, Dr. Klein reviewed **DMF** — and found the — adequate on 11/21/2008. b(4)

Because the oral suspension will be formulated by the pharmacist, the suspension will be provided to the patient in an amber ⌐ ⊥ bottle with a child resistant closure. These are standard packaging systems in US pharmacies. b(4)

The following stability studies were conducted to support the stability of the respective oral suspensions in an amber [ ] bottle for 14 days at 2°C – 8°C *(to be stated on the bottle's label)*: b(4)

1. Long term conditions at 5°C.
2. Accelerated conditions at 25°C/60%RH.
3. Stressing conditions at 50°C and light exposure (photostability).
4. Stored at 5°C and shaken daily to simulate daily use.
5. Stored at 5°C with a reduced volume of oral suspension (50 mL instead of 200 mL) to determine the effect of a large bottle headspace.
6. Freeze-thaw (2x) temperature cycling at -20°C for 48 hrs and 25°C for 48 hrs.

Drug Substances

Bicalutamide

NDA 20-498 *(approved 10/1995)* Casodex® (bicalutamide) Immediate Release Tablet (50 mg) is referenced.

Because the applicant has proposed an oral suspension, the following drug substance properties are useful in the evaluation of the bicalutamide oral suspension:

1. Bicalutamide is poorly soluble in aqueous media at the physiological pH range; specifically, the solubility is 3.7 mg/L to 4.6 mg/L from pH 1 to pH 8 at 37°C.
2. Bicalutamide is lipophilic and bicalutamide has been shown to be rapidly absorbed throughout the GI tract when in solution in an *in situ* rat gut loop model. The absorption of bicalutamide is considered to be dissolution rate limited.

Anastrozole

NDA 20-541 *(approved 12/1995)* Arimidex® (anastrozole) Immediate Release Tablet (1 mg) is referenced.

Because the applicant has proposed an oral suspension, the following drug substance properties are useful in the evaluation of the anastrozole oral suspension:

1. Anastrozole is highly soluble across the physiological pH range; specifically, the solubility is 0.6 mg/mL to 2.7 mg/mL at pH 1 to pH 8 at 25°C.
2. Anastrozole has low dose: solubility ratios; specifically, 0.4 to 1.7 at pH 1 to pH 8.
3. Anastrozole aqueous solution has been shown to rapidly absorbed throughout the GI tract in a rat gut loop model.

B. Description of How the Drug Product is Intended to be Used:

The only section of the draft labeling that requires evaluation from the CMC perspective is:

8. USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use

b(4)

b(4)

C. Basis for Approvable or Not-Approval Recommendation:

NDA 22-310 is recommended approval.

D. Administrative:

ONDQA Reviewer, Branch 7 : Donald N. Klein, Ph.D.
ONDQA PAL, Branch 7: Janice Brown.
ONDQA Branch Chief, Branch 7: James Vidra, Ph.D.
ONDQA Project Manager, Branch 7: Rebecca McKnight, B.S.
ONDQA Project Manager, Branch 7: Melissa Fratine. M.S.
OND Project Manager, HFD-510: Jennifer Johnson.

19 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

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

/s/

Donald Klein
12/11/2008 10:26:46 AM
CHEMIST

OND Request: Review to be completed by 12/12/08; DUE date is 12/25/08.

Jim Vidra
12/11/2008 02:50:38 PM
CHEMIST

8/4/08

Filing Memorandum

Date: 04-Aug-2008
From: Janice Brown, Pharmaceutical Assessment Lead, Branch VII/DPME/ONDQA
To: NDA 22-310

Supplement provides for: A Type 6 NDA that provides safety, efficacy and pharmacokinetic information on the use of CASODEX→ (bicalutamide) in combination with Arimidex→ (anastrozole) in male pubertal patients with testotoxicosis.

Background
This NDA describes separate oral suspension formulations of bicalutamide and anastrozole that are compounded to produce the final dosage form. ⌜

b(4)

⌟

The preparation of CASODEX Oral Suspension 10 mg/mL is compounded by taking the

⌜

b(4)

⌟

ARIMIDEX Oral Suspension 0.2 mg/mL is compounded by taking the required number of

⌜

b(4)

⌟

Filing Comments

- The applicant has cross referenced the drug substance [and drug product] anastrozole supplied in the form of ARIMIDEX 1 mg tablets in NDA 20-541.
- The applicant has cross referenced the drug substance [and drug product] bicalutamide supplied in the form of CASODEX 50 mg tablets in NDA 20-498.
- A LOA for DMF No. ⌜ ⌟ was provided. b(4)

- Comparative dissolution profiles were provided using the commercial CASODEX tablet and the compounded suspension.

- Dissolution profiles have also been generated for the commercial 1 mg ARIMIDEX tablet, [ ], and a 1 mg dose of the extemporaneously prepared suspension (5 mL). b(4)

- Stability data (three batches) was provided for ARIMIDEX Oral Suspension compounded from ARIMIDEX 1 mg tablets [ ] for 14 days when stored 2°C - 8°C (36°F and 46°F). b(4)

- Stability data (three batches) was provided for CASODEX Oral Suspension compounded from CASODEX 50 mg tablets [ ] for 14 days when stored at 2°C - 8°C (36°F and 46°F). b(4)

- AstraZeneca requests a categorical exclusion from the need to prepare an environmental assessment in accordance with 21 CFR 25.31 (a) or (b).

- Labeling was provided.

Conclusion:

From a CMC standpoint, this NDA can be filed.

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/s/

Janice Brown
8/4/2008 01:24:50 PM
CHEMIST