

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-310

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER
022-310
NAME OF APPLICANT / NDA HOLDER
AstraZeneca UK Limited

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Casodex®

ACTIVE INGREDIENT(S)
bicalutamide

STRENGTH(S)
50 mg

DOSAGE FORM
tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number 4,636,505	b. Issue Date of Patent January 13, 1987	c. Expiration Date of Patent October 1, 2008
d. Name of Patent Owner AstraZeneca UK Limited	Address (of Patent Owner) 15 Stanhope Gate	
	City/State London, UK	
	ZIP Code W1K 1LN	FAX Number (if available) +44 (0)20 7304 5151
	Telephone Number +44 (0)20 7304 5000	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Glenn M. Engelmann, Vice President, Policy, Legal & Scientific Affairs & General Counsel, AstraZeneca Pharmaceuticals LP	Address (of agent or representative named in 1.e.) 1800 Concord Pike	
	City/State Wilmington, DE	
	ZIP Code 19850-5437	FAX Number (if available) (302) 886-1578
	Telephone Number (800) 456-3669	E-Mail Address (if available) glenn.engelmann@astrazeneca.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? <input type="checkbox"/> Yes <input type="checkbox"/> No		

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
 *Certain claims may cover at least one additional polymorph in addition to claiming the drug substance of the pending NDA, amendment, or supplement, but the patent is not being listed on that basis.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

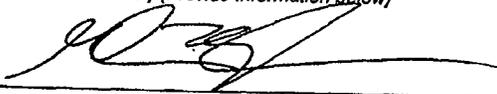
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



6/9/08

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Glenn Engelmann, Vice President, Policay, Legal & Scientific Affairs & General Counsel

Address

1800 Concord Pike

City/State

Wilmington, DE

ZIP Code

19803

Telephone Number

(302) 886-3244

FAX Number (if available)

(302) 886-1578

E-Mail Address (if available)

glenn.engelmann@astrazeneca.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.

Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

12/19/08

EXCLUSIVITY SUMMARY

NDA # NDA 22-310

SUPPL # N/A

HFD # 510

Trade Name Casodex

Generic Name bicalutamide

Applicant Name AstraZeneca Pharmaceuticals LP

Approval Date, If Known December 19, 2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

.505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Pediatric exclusivity determination requested (6 months); sponsor not seeking an indication or other type of exclusivity

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

yes

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-498

Casodex (bicalutamide) Tablets, 50 mg

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

N/A

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

N/A

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

N/A

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation 1: Study D6873C00003 (A relative bioavailability study between a pediatric bicalutamide oral liquid or dispersible tablet formulation and the marketed 50 mg bicalutamide oral tablet)

Investigation 2: Study D6873C00002 (A relative bioavailability study between a pediatric anastrozole oral liquid or dispersible tablet formulation and the marketed 1 mg anastrozole oral tablet)

Investigation 3: Study D6873C000047 (An open-label efficacy and safety study of bicalutamide when used in combination with anastrozole for the treatment of precocious puberty in boys with testotoxicosis)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #3 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

N/A

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation 1: Study D6873C00003 (A relative bioavailability study between a pediatric bicalutamide oral liquid or dispersible tablet formulation and the marketed 50 mg bicalutamide oral tablet)

Investigation 2: Study D6873C00002 (A relative bioavailability study between a pediatric anastrozole oral liquid or dispersible tablet formulation and the marketed 1 mg anastrozole oral tablet)

Investigation 3: Study D6873C000047 (An open-label efficacy and safety study of bicalutamide when used in combination with anastrozole for the treatment of precocious puberty in boys with testotoxicosis)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 61,238 YES ! NO
! Explain:

Investigation #2
IND # 61,238 YES ! NO
! Explain:

Investigation #3
IND # 61,238 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
YES ! NO
Explain: ! Explain:

Investigation #2
YES ! NO
Explain: ! Explain:

Investigation #3
YES ! NO
! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

N/A

Name of person completing form: Jennifer Johnson
Title: Regulatory Project Manager
Date: December 19, 2008

Name of Office/Division Director signing form: Mary H. Parks, M.D.
Title: Director, Division of Metabolism and Endocrinology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Mary Parks
12/19/2008 03:50:07 PM

12/15/08

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-310 Supplement Number: N/A NDA Supplement Type (e.g. SE5): N/A

Division Name: Metabolism and Endocrinology Products PDUFA Goal Date: 12/25/08 Stamp Date: 6/25/2008

Proprietary Name: Casodex

Established/Generic Name: bicalutamide

Dosage Form: Tablets

Applicant/Sponsor: AstraZeneca Pharmaceuticals LP

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):
(1) For use in combination therapy with a luteinizing hormone-releasing hormone (LHRH) analog for the treatment of Stage D2 metastatic carcinoma of the prostate.

(2) _____

(3) _____

(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

Indication: None sought by applicant – studies conducted in response to a Pediatric Written Request – Casodex studied in combination with Arimidex for the treatment of gonadotropin-independent precocious puberty in boys with familial male-limited precocious puberty (testotoxicosis)

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 - No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Jennifer Johnson
Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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

/s/

Jennifer Johnson
12/15/2008 04:28:10 PM



1.3.3 DEBARMENT CERTIFICATION

Re: NDA 22-310
CASODEX® (bicalutamide) Tablets
Debarment Certification Statement

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of AstraZeneca Pharmaceuticals LP (AstraZeneca), that we did not use and will not use in connection with this New Drug Application, the services of any person in any capacity debarred under section 306 (a) or (b).

Sincerely,

A handwritten signature in cursive script, appearing to read "Anthony Rogers", written over a horizontal line.

Anthony Rogers, Vice President
Regulatory Affairs
AstraZeneca

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

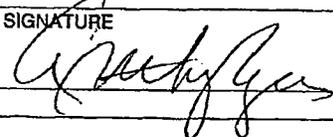
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	SEE ATTACHED REPORT(S)	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Anthony Rogers	TITLE Vice President, Regulatory Affairs
FIRM / ORGANIZATION AstraZeneca Pharmaceuticals	
SIGNATURE 	DATE 6/16/08

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

6 Page(s) Withheld

Trade Secret / Confidential (b6)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

7/8/08



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-310

NDA ACKNOWLEDGMENT

AstraZeneca Pharmaceuticals LP
Attention: Cindy Lancaster, M.S., J.D.
Executive Director, Regulatory Affairs
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Lancaster:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Casodex (bicalutamide) Tablets

Date of Application: June 25, 2008

Date of Receipt: June 25, 2008

Our Reference Number: NDA 22-310

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **August 24, 2008**, in accordance with 21 CFR 314.101(a).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-310
Page 2

If you have any questions, please call me at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Jennifer Johnson
7/8/2008 06:46:52 PM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22-310	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Casodex Established/Proper Name: bicalutamide Dosage Form: Tablets		Applicant: AstraZeneca Pharmaceuticals LP Agent for Applicant (if applicable): N/A
RPM: Jennifer Johnson		Division: HFD-510
NDA: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): N/A Provide a brief explanation of how this product is different from the listed drug. N/A <input type="checkbox"/> If no listed drug, check here and explain: Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review. <input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug. On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.
❖ User Fee Goal Date Action Goal Date (if different)		December 25, 2008 December 19, 2008
❖ Actions		
<ul style="list-style-type: none"> • Proposed action 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
❖ Promotional Materials (<i>accelerated approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application ² Characteristics	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): 6 <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: _____	December 10, 2008 (determined that PREA not triggered by this application)
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

<p>• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.</p> <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).</p> <p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p> <p>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.</i></p> <p><i>If "No," continue with question (3).</i></p> <p>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).</p> <p><i>If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.</i></p> <p>(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "No," continue with question (5).</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
---	---

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ³	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	Included
Documentation of consent/non-consent by officers/employees	Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval letter dated December 19, 2008
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	December 17, 2008 (pediatric language by the Division of Metabolism and Endocrinology Products); December 14, 2008 (by parent NDA 20-498 in the Division of Drug Oncology Products)
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	November 5, 2008 (to parent NDA 20-498 in the Division of Drug Oncology Products)
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	October 25, 2007 (to parent NDA 20-498 in the Division of Drug Oncology Products); labeling

³ Fill in blanks with dates of reviews, letters, etc.
Version: 9/5/08

	submitted to original NDA submission dated June 25, 2008, in the Division of Metabolism and Endocrinology Products
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	N/A
<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	December 14, 2008 (by parent NDA 20-498 in the Division of Drug Oncology Products)
<ul style="list-style-type: none"> Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	November 5, 2008 (to parent NDA 20-498 in the Division of Drug Oncology Products)
<ul style="list-style-type: none"> Original applicant-proposed labeling 	October 25, 2007 (to parent NDA 20-498 in the Division of Drug Oncology Products); labeling submitted to original NDA submission dated June 25, 2008, in the Division of Metabolism and Endocrinology Products
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	N/A
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> Most-recent division proposal for (only if generated after latest applicant submission) 	Approved under NDA 20-498
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	Approved under NDA 20-498
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input type="checkbox"/> DMEDP <input type="checkbox"/> DRISK <input type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> Review(s) (<i>indicate date(s)</i>) Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	Approved under NDA 20-498 N/A
Administrative/Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	September 22, 2008
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	December 19, 2008
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html 	
<ul style="list-style-type: none"> Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.
Version: 9/5/08

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	December 15, 2008
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing communications (<i>if located elsewhere in package, state where located</i>) • Incoming submissions/communications 	
❖ Postmarketing Commitment (PMC) Studies	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>) • Incoming submission documenting commitment 	
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	July 8, August 12, 18, 27, September 3 and 19, November 19 and 25, 2008
❖ Internal memoranda, telecons, etc.	None
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • PeRC (<i>indicate date; approvals only</i>) 	Pending
<ul style="list-style-type: none"> • Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Regulatory Briefing (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date</i>) 	<input type="checkbox"/> No mtg (Held clarification teleconference on February 1, 2008 regarding the Pre-NDA responses issued on January 22, 2008, in lieu of formal meeting – final minutes pending)
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Other (e.g., EOP2a, CMC pilot programs) 	PPSR Denial clarification meeting (teleconference): September 20, 2006
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) • 48-hour alert or minutes, if available 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁵	

Filing reviews should be filed with the discipline reviews.
Version: 9/5/08

❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	Concurrence by Team Leader on the primary review dated December 15, 2008
• Clinical review(s) (indicate date for each review)	December 15, 2008
• Social scientist review(s) (if OTC drug) (indicate date for each review)	X None
❖ Safety update review(s) (indicate location/date if incorporated into another review)	See page 50 of clinical review
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	December 15, 2008
❖ Clinical reviews from other clinical areas/divisions/Centers (indicate date of each review)	X None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	X Not needed
❖ Risk Management <ul style="list-style-type: none"> • Review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review) • REMS Memo (indicate date) • REMS Document and Supporting Statement (indicate date(s) of submission(s)) 	X None
❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	X None requested
Clinical Microbiology X None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	X None
Statistical Team Leader Review(s) (indicate date for each review)	X None
Statistical Review(s) (indicate date for each review)	December 17, 2008
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	X None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	Concurrence by Team Leader on the primary review dated December 15, 2008
Clinical Pharmacology review(s) (indicate date for each review)	December 15, 2008
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	X None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	X None
• Supervisory Review(s) (indicate date for each review)	X None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	November 14, 2008
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	X None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	X No carc

❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	Concurrence by Team Leader on the primary review dated December 11, 2008 and on DMF review dated November 21, 2008
• CMC/product quality review(s) (indicate date for each review)	December 11, 2008 November 21, 2008 (DMF 14443) August 4, 2008 (Filing Review)
• BLAs only: Facility information review(s) (indicate dates)	N/A
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	October 31, 2008
• BLAs: Sterility assurance, product quality microbiology (indicate date of each review)	N/A
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	December 11, 2008
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) (date completed must be within 2 years of action date)	Date completed: N/A <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
• BLAs:	
○ TBP-EER	Date completed: N/A <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (date completed must be within 60 days prior to AP)	Date completed: N/A <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) Or it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) Or it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) Or the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) Or the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

/s/

Jennifer Johnson
12/22/2008 02:51:22 PM

DFS 12/3/08

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Tuesday, November 25, 2008 11:04 AM
To: 'Valas, E Jane'
Cc: Johnson, Jennifer
Subject: RE: Casodex NDA 22-310: Reviewer Questions - Additional Request for Information

Hello Jane,

We have an another CMC request for information, in addition to those sent via email on November 19, 2008.

Please refer to the respective stability sections of the two oral suspensions. In several instances No Individual Impurity (NIG) is presented for the Total Degradation Products at the 7 day and 14 day time point. Revise the respective stability tables with the correct total value of the degradation product. In the event NIG refers to "no increase in degradation from the initial value", then provide a brief statement in your response.

Please submit your response officially to NDA 22-310 - you may include responses to this question and the previous questions (listed below) in the same NDA amendment if you wish.

Let me know if you have any questions.

Many thanks,
Jennifer

From: Johnson, Jennifer
Sent: Wednesday, November 19, 2008 2:08 PM
To: 'Valas, E Jane'
Cc: Johnson, Jennifer
Subject: Casodex NDA 22-310: Reviewer Questions

Good afternoon Jane,

We have two questions for you regarding Casodex NDA 22-310.

1. Please refer to the stability section of each drug product in NDA 22-310.
 - a. Was pH monitored on stability testing? Either provide the respective stability data or provide justification for not monitoring pH.
 - b. Was the container always in the upright position on stability testing? In the event the container was on its side, please indicate the stability test(s).

Please reply in an official submission to NDA 22-310.

Let me know if you have any questions.

Many thanks,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration

12/3/2008

301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

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this page is the manifestation of the electronic signature.**

/s/

Jennifer Johnson
12/3/2008 03:42:03 PM
CSO

DFS 11/21/08

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Wednesday, November 19, 2008 2:08 PM
To: 'Valas, E Jane'
Cc: Johnson, Jennifer
Subject: Casodex NDA 22-310: Reviewer Questions

Good afternoon Jane,

We have two questions for you regarding Casodex NDA 22-310.

1. Please refer to the stability section of each drug product in NDA 22-310.
 - a. Was pH monitored on stability testing? Either provide the respective stability data or provide justification for not monitoring pH.
 - b. Was the container always in the upright position on stability testing? In the event the container was on its side, please indicate the stability test(s).

Please reply in an official submission to NDA 22-310.

Let me know if you have any questions.

Many thanks,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

11/21/2008

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this page is the manifestation of the electronic signature.**

/s/

Jennifer Johnson
11/21/2008 05:31:19 PM
CSO

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # 22-310 BLA# N/A	NDA Supplement #:S- N/A BLA STN # N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Casodex Established/Proper Name: bicalutamide Dosage Form: Tablets Strengths: 50 mg		
Applicant: AstraZeneca UK Limited Agent for Applicant (if applicable): AstraZeneca Pharmaceuticals LP		
Date of Application: June 25, 2008 Date of Receipt: June 25, 2008 Date clock started after UN: N/A		
PDUFA Goal Date: December 25, 2008	Action Goal Date (if different): December 18, 2008	
Filing Date: August 24, 2008 Date of Filing Meeting: August 4, 2008		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 6		
Proposed Indication(s): <i>N/A (applicant not seeking an indication – only Pediatric Exclusivity Determination)</i>		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: N/A <i>Refer to Appendix A for further information.</i>	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical disease Priority review voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR	

601.42)	
Collaborative Review Division (<i>if OTC product</i>):	
List referenced IND Number(s): 61, 238	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aip.html</i> If yes, explain: N/A If yes, has OC/DMPQ been notified of the submission? N/A Comments: N/A	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status Comments: User Fee ID 3008439	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	

<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p> <p>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments: N/A</p>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p># years requested: <input checked="" type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? *Check the Electronic Orange Book at: <http://www.fda.gov/cder/ob/default.htm>*

YES
 NO

If yes, please list below:

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content

Do not check mixed submission if the only electronic component is the content of labeling (COL).

Comments:

All paper (except for COL)
 All electronic
 Mixed (paper/electronic)

CTD
 Non-CTD
 Mixed (CTD/non-CTD)

If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?

N/A

If electronic submission:
paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)?

YES
 NO

Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.

Comments: Field copy certification and pediatric waiver documents not signed (but are included in application)

If electronic submission, does it follow the eCTD guidance? (<http://www.fda.gov/cder/guidance/7087rev.pdf>)

YES
 NO

If not, explain (e.g., waiver granted):

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments: Establishments and registration numbers are contained within the application</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</p> <p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p> <p>Comments:</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Pediatrics	
<p>PREA</p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> <p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) 	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

<p>Comments: <i>The applicant submitted a partial waiver for ages 2-12 years (but included ages 2-9 years in its studies). The applicant was requested in the 74-day letter to address the age ranges 0-1 and 13-16 years. The applicant responded by submitting a full waiver of pediatric studies.</i></p>	
<p>BPCA (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i></p> <p>Comments: Pediatric Exclusivity Board meeting scheduled for August 19, 2008</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
Prescription Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<p><input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)</p>
<p>Is electronic Content of Labeling submitted in SPL format?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Package insert (PI) submitted in PLR format?</p> <p><i>If no, was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request?</i></p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?</p> <p>Comments: <i>N/A – Division of Drug Oncology Products (DDOP) responsible for this consult (parent division)</i></p>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)</p> <p>Comments: <i>Division of Drug Oncology Products (DDOP) responsible for this consult (parent division)</i></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p>

REMS consulted to OSE/DRISK? Comments: <i>Division of Drug Oncology Products (DDOP) responsible for this consult (parent division)</i>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? Comments: <i>Division of Drug Oncology Products (DDOP) responsible for this consult (parent division)</i>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

OTC Labeling	
Check all types of labeling submitted. Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
Is electronic content of labeling submitted? <i>If no, request in 74-day letter.</i> Comments:	<input type="checkbox"/> YES <input type="checkbox"/> NO
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i> Comments:	<input type="checkbox"/> YES <input type="checkbox"/> NO
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i> Comments:	<input type="checkbox"/> YES <input type="checkbox"/> NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? Comments:	<input type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? <i>If yes, distribute minutes before filing meeting.</i> Comments:	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <i>If yes, distribute minutes before filing meeting.</i>	<input type="checkbox"/> YES Date(s):

<p>Comments: The applicant requested a Pre-NDA meeting under IND 61,238 on September 26, 2007. The meeting was denied on October 10, 2007 (the Division opted to respond in writing instead following submission of the Pre-NDA meeting background package, which was submitted on October 31, 2007), and written responses were provided on January 22, 2008. The applicant submitted a meeting (teleconference) request on January 24, 2008, to discuss and clarify the Division's responses. A teleconference was held on February 1, 2008 (minutes of that teleconference are still pending and expect to be issued soon).</p>	<p>X NO</p>
<p>Any Special Protocol Assessment (SPA) agreements? <i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments:</p>	<p><input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO</p>

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 4, 2008

NDA/BLA #: 22-310

PROPRIETARY/ESTABLISHED NAMES: Casodex (bicalutamide) Tablets

APPLICANT: AstraZeneca Pharmaceuticals LP

BACKGROUND:

Casodex is a non-steroidal antiandrogen approved in the Division of Drug Oncology Products (DDOP) under NDA 20-498 for the use in combination therapy with a luteinizing hormone-releasing hormone (LHRH) analogue for the treatment of Stage D2 metastatic carcinoma of the prostate. This drug was originally approved in the Division of Reproductive and Urologic Products but then transferred to DDOP in October 2005. Casodex is available as a 50 mg tablet.

The sponsor submitted a Proposed Pediatric Study Request (PPSR) to IND 61,238 in the Division of Metabolism and Endocrinology Products (DMEP) on October 25, 2001. This PPSR proposed the use of Casodex in combination with Arimidex (an aromatase inhibitor) for the treatment of familial male-limited precocious puberty (testotoxicosis) in boys, and was denied on March 12, 2002. The sponsor submitted a revised PPSR on December 13, 2002, and a Pediatric Written Request (WR) was issued on April 17, 2003. The WR was subsequently amended on February 13, May 7, October 1, 2004, April 8, 2005, and February 7 and May 9, 2008.

The WR Amendment #6 (issued on May 9, 2008) provides the basis for this Type 6 NDA 22-310, submitted on June 25, 2008 (including final clinical study reports), to DMEP for the purpose of Pediatric Exclusivity Determination.

Representatives of DMEP met with the Pediatric Exclusivity Board on September 16, 2008.

Pediatric Exclusivity was granted for the active moiety bicalutamide on September 19, 2008.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jennifer Johnson	Y
	CPMS/TL:	Lina AlJuburi	Y
Cross-Discipline Team Leader (CDTL)	N/A		
Clinical	Reviewer:	Dragos Roman	Y
	TL:	Mary Parks	Y

Social Scientist Review (for OTC products)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Labeling Review (for OTC products)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OSE	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Microbiology (for antimicrobial products)	Reviewer:	N/A	N/A
	TL:	N/A	N/A

Clinical Pharmacology	Reviewer:	Lucun Bi	Y
	TL:	Sally Choe	Y
Biostatistics	Reviewer:	Todd Sahlroot	Y
	TL:	Todd Sahlroot	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Karen Davis Bruno	Y
	TL:	Karen Davis Bruno	Y
Statistics, carcinogenicity	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Product Quality (CMC)	Reviewer:	Donald Klein	N
	TL:	James Vidra (PAL: Janice Brown)	N Y
Facility (for BLAs/BLA supplements)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Microbiology, sterility (for NDAs/NDA efficacy supplements)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Bioresearch Monitoring (DSI)	Reviewer:	N/A	N/A

OTHER ATTENDEES: Susan Liebenhaut (assigned DSI clinical reviewer – DSI audits determined to be not needed), Ritesh Jain, Immo Zdrojewski

<p>505(b)(2) filing issues?</p> <p>If yes, list issues:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Per reviewers, are all parts in English or English translation?</p> <p>If no, explain:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Electronic Submission comments</p> <p>List comments: <i>None</i></p>	<p><input type="checkbox"/> Not Applicable</p>
<p>CLINICAL</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter</p>
<p>• Clinical study site(s) inspections(s) needed?</p> <p>If no, explain: <i>This is a negative clinical study.</i></p>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<p>• Advisory Committee Meeting needed?</p> <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p><input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined</p> <p>Reason:</p>
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter</p>

<p>CLINICAL PHARMACOLOGY</p> <p><i>Comments: Method validation reports not included in application; will request in 74-day letter.</i></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p><i>Comments:</i></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p><i>Comments:</i></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p><i>Comments:</i></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p><i>Comments:</i></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p><i>Comments:</i></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>• Sterile product? <i>(The drug tablet under review is not a sterile product but the oral suspension formulations of bicalutamide and anastrozole were compounded and dispersed in _____ for use in the studies; therefore,, a micro review will be needed to re-review the _____ described in DMF _____ per CMC reviewer request; consult to Microbiology completed on August 5, 2008, by CMC RPM.)</i></p> <p>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</p>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>FACILITY (BLAs only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter</p>
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Mary Parks</p> <p>GRMP Timeline Milestones: Filing meeting scheduled for August 4, 2008, Mid-cycle review meeting TBD, PDUFA Goal Date: December 25, 2008</p> <p>Comments: None</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTIONS/ITEMS	
<p><input checked="" type="checkbox"/></p>	<p>Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.</p>
<p><input type="checkbox"/></p>	<p>If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.</p>

b(4)

<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and,
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

Jennifer Johnson
9/22/2008 05:21:44 PM
CSO

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Friday, September 19, 2008 5:27 PM
To: 'Valas, E Jane'
Cc: 'Troise, Nicholas J'
Subject: Pediatric Exclusivity Granted for Bicalutamide

Dear Dr. Valas,

Pediatric Exclusivity has been granted for studies conducted on bicalutamide, effective September 19, 2008, under section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a), as amended by the Best Pharmaceuticals for Children Act (BPCA). This information will be reflected on CDER's pediatric web site and in the monthly update of the Orange Book. For additional information, please see the Guidance for Industry - Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act (<http://www.fda.gov/cder/guidance/2891fni.pdf>).

In accordance with section 505A(e)(1) of the Act, as amended by FDAAA (Pub. L. No. 110-85), approved drugs for which a pediatric exclusivity determination was made, on or after September 27, 2007, shall have a copy of the Written Request and any amendments posted on CDER's pediatric web site.

In addition, we remind you that section 17 of the BPCA, as reauthorized and amended under the FDA Amendments Act of 2007, requires for one year after pediatric labeling is approved, any report received by FDA of an adverse event associated with the drug granted exclusivity will be referred to the Office of Pediatric Therapeutics. This process occurs for all products granted Pediatric Exclusivity regardless of the regulatory action taken. The Director of that Office will provide for a review of the adverse event reports by the Pediatric Advisory Committee (PAC) and will obtain recommendations from that Committee on action FDA should take.

Please contact me with any questions or concerns.

Many thanks,

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

9/19/2008

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this page is the manifestation of the electronic signature.**

/s/

Jennifer Johnson
9/19/2008 05:31:12 PM
CSO

DFS 9/19/08

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA 4/17/03

WR Amendment 1 2/13/04 WR Amendment 2 5/7/04

WR Amendment 3 10/1/04 WR Amendment 4 4/8/05

WR Amendment 5 2/7/08 WR Amendment 6 5/9/08

Application Written Request was made to: IND# 61,238

Timeframe Noted in Written Request for Submission of Studies 6/30/08

NDA# 22-310 Supplement # N/A Choose one: SB1 SB2 SB3 SB4 SB5 SB6 SB7 SB8 SLR

Sponsor AstraZeneca Pharmaceuticals LP

Generic Name bicalutamide Trade Name Casodex

Strength 50 mg Dosage Form/Route Tablets

Date of Submission of Reports of Studies 6/25/08

Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 9/23/08

Was a formal Written Request made for the pediatric studies submitted?	<u>Y X</u>	<input checked="" type="checkbox"/>
Were the studies submitted after the Written Request?	<u>Y X</u>	<input checked="" type="checkbox"/>
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	<u>Y X</u>	<input type="checkbox"/>
Was the timeframe noted in the Written Request for submission of studies met?	<u>Y X</u>	<input checked="" type="checkbox"/>
If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	<u>Y X</u>	<input checked="" type="checkbox"/>
Did the studies fairly respond to the Written Request?	<u>Y X</u>	<input checked="" type="checkbox"/>

SIGNED *Maqen Roman*
(Reviewing Medical Officer)

DATE 9/10/2008

SIGNED *Mary Clark*
(Division Director)

DATE 9/10/2008

Do not enter in DFS - FORWARD TO PEDIATRIC EXCLUSIVITY BOARD via Pediatric and Maternal Health Team PM

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity Granted Denied

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
<u>20-498</u>	<u>4636505</u>	<u>Oct 1, 2008</u>

SIGNED *[Signature]*
(Last revised June 30, 2005)

DATE 9/16/08

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this page is the manifestation of the electronic signature.**

/s/

John Jenkins
9/19/2008 03:32:14 PM

Contains email information requests for information
(August 12, 18, 27, 2008)

Page 1 of 5

DFS 9/18/08

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Wednesday, August 27, 2008 3:29 PM
To: Troise, Nicholas J
Cc: 'Valas, E Jane'; Johnson, Jennifer
Subject: RE: Review Team Questions: NDA 22-310 (Casodex)

Good afternoon Nick,

We have finished reviewing your last submission dated 8/21/08, in response to our information request dated 8/18/08.

We just need two more pieces of information from you:

1. Provide the results of the baseline GnRH stimulation tests performed at local laboratories for patients E002001 and E0013004.
2. Clarify why the Timepoint 2 was "deleted" in the baseline GnRH stimulation test for patient E003002.

Please feel free to contact me if you have any questions.

Many thanks for your help,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

From: Valas, E Jane [mailto:jane.valas@astrazeneca.com]
Sent: Thursday, August 21, 2008 4:52 PM
To: Johnson, Jennifer
Subject: RE: Review Team Questions: NDA 22-310 (Casodex)

Jennifer,

Here is a copy of response to query 1 submitted today to NDA 22-310 through FDA's electronic Gateway. I'm thinking that submission may not have gotten totally thru Gateway prior to 4:30 so it may not be available to you via Gateway until tomorrow.

Please be advised that I will be on vacation next week. Nick Troise will be available should there be any questions.

Kind regards,
Jane

-----Original Message-----

From: Valas, E Jane
Sent: Tuesday, August 19, 2008 6:00 PM

9/18/2008

To: 'Johnson, Jennifer'
Subject: RE: Review Team Questions: NDA 22-310 (Casodex)

Dear Jennifer,

Here is a copy of response to query 2 submitted today to NDA 22-310 through FDA's electronic Gateway. Response to query 1 will be submitted tomorrow.

Kind regards,
Jane

-----Original Message-----

From: Johnson, Jennifer [mailto:jennifer.johnson@fda.hhs.gov]
Sent: Monday, August 18, 2008 6:27 PM
To: Valas, E Jane
Cc: Johnson, Jennifer
Subject: RE: Review Team Questions: NDA 22-310 (Casodex)

Hello Jane,

Thanks again for sending the necessary information so quickly - it was very helpful.

We do have 2 additional requests in response to your 8/15/08 submission.

1. Please provide us with additional data as a follow-up to our preceding information request. We would like to know more about the results of the tests performed at the local laboratories that allowed the local investigators to arrive at the conclusions described in your 8/15/08 submission (in particular, those related to the GnRH stimulation test at or prior to screening).
2. Please also provide a list of the patients who had a diagnosis of testotoxicosis made by genetic testing.

If you have any questions about the above requests, please feel free to contact me.

Kind Regards,
Jennifer

From: Valas, E Jane [mailto:jane.valas@astrazeneca.com]
Sent: Friday, August 15, 2008 1:11 PM
To: Johnson, Jennifer
Subject: RE: Review Team Questions: NDA 22-310 (Casodex)

Hello, Jennifer,

This is to inform you that notification of receipt by FDA's Gateway of AZ's response has been received.

Per your request, here is a copy for your use.

Please contact me if further information is needed.

Kind regards,
Jane
302-886-2122

-----Original Message-----

From: Johnson, Jennifer [mailto:jennifer.johnson@fda.hhs.gov]

Sent: Thursday, August 14, 2008 1:32 PM
To: Valas, E Jane
Subject: RE: Review Team Questions: NDA 22-310 (Casodex)

Hello Jane,

Thanks for your prompt response - we really appreciate it, as well as directing us to the data location for our statistical query #2.
We look forward to receiving the remaining information from you on Friday.

Kind Regards,
Jennifer

From: Valas, E Jane [mailto:jane.valas@astrazeneca.com]
Sent: Wednesday, August 13, 2008 7:09 PM
To: Johnson, Jennifer
Subject: RE: Review Team Questions: NDA 22-310 (Casodex)

Hello, Jennifer,

The Casodex team has agreed that responses to these points of clarification will be available Friday for submission. I will plan on sending the responses to you via e-mail and officially to the NDA.

I would ask you to share now with the Statistician (Todd Sahlroot?) that the data requested in Statistical query #2 "height SD scores" is already in the submission in Module 5.3.5.2 under d6873c00047 dataset **rd_hght.xpt** with identified variables being the following :

Median	Median from the updated growth chart
SD	Standard deviation from the updated growth chart
SDS	SD score
GROWTHSD	Growth Rate (in SD units)
GRSDSCBL	Change from baseline in SD units
MTHFTRT	Derived assessment visit

Would you be able to check to see if the Statistician is able to "find" this dataset?

Thank you,
Jane

-----Original Message-----

From: Johnson, Jennifer [mailto:jennifer.johnson@fda.hhs.gov]
Sent: Tuesday, August 12, 2008 2:59 PM
To: Valas, E Jane
Cc: Troise, Nicholas J
Subject: Review Team Questions: NDA 22-310 (Casodex)

Good afternoon Jane,

We are currently reviewing the pediatric NDA 22-310 for Casodex, and have the following clinical and statistical (data clarification and additional electronic data) information requests for Study D6873C00047:

Clinical

According to the inclusion criterion # 3 of the Study D6873C00047 clinical protocol, patients had to have a diagnosis of testotoxicosis based on the following:

- clinical features (progressive sexual precocity documented by Tanner staging and evidence of symmetrical testicular enlargement, and bone age advanced at least > 12 months over chronological age)
- pubertal levels of serum testosterone
- prepubertal levels of serum gonadotropins
- lack of an increase in serum gonadotropin levels following GnRH stimulation
- exclusion of other causes of precocious puberty (normal plasma beta-human chorionic gonadotropin, normal 17-hydroxyprogesterone, normal levels of dehydroepiandrosterone sulphate).

According to pages 2 and 3 of the CRF, these criteria were to be met at Visit 1 and the following statement was included on Page 3 of the CRF: "If No to any Inclusion criteria, please withdraw Subject and fill in TERM, Withdrawal Section".

Please explain why the following patients were enrolled in the trial given the following:

- Patient E0003002 did not have baseline GnRH stimulation testing results recorded and the presence or absence of CPP could not be assessed (Appendix 12.2.8.11 Listing of GnRH stimulation).
- Patient E0009001 had a maximum stimulated LH level > 4 U/L (4.1 U/L) at baseline (Appendix 12.2.8.11) and an elevated 17-OH progesterone of 2.70 nmol/L at baseline (repeat 2.40 nmol/L on Day 1) (Appendix 12.2.8.10 Listing of sex hormones (II)).
- Patient E0013001 had a maximum stimulated LH level > 4 U/L (6.7 and 6.3 U/L) at baseline (Appendix 12.2.8.11)
- Patient E0023001 did not have an elevated total testosterone on Day 1 (4.08 nmol/L; Appendix 12.2.8.9 Listing of sex hormones(I)), had no GnRH stimulation test recorded at baseline (Appendix 12.2.8.11), did not have β -HCG, DHAES and 17-hydroxy progesterone measured at baseline to exclude other pathologies (Appendix 12.2.8.10).
- Patient E0052001 did not have baseline GnRH stimulation testing results to confirm or exclude CPP (Appendix 12.2.8.11).
- Patients E0054003 and E0054004 did not have baseline DHAES and 17-hydroxy progesterone measurements baseline to exclude other pathologies (Appendix 12.2.8.10).
- Patient E0057001 had a baseline 17-hydroxy progesterone of 3.19 nmol/L which was above the upper limit of normal (Appendix 12.2.8.10).

Statistical

1. Pre-study height data for patients E0054003 and E0054004 (twins) were collected on 12/09/04 and 10/18/06. These dates were 871 and 193 days prior to Visit 1 (baseline). The 12/9/04 data were used to compute pre-study growth rates although the 10/18/06 data were the most recent pre-study height data measured at least six months prior to the start of the study. Why were the 10/18/06 data not used to calculate the pre-study growth rates for these two patients?
2. Please submit SAS transport dataset(s) with height SD scores. The format should be similar to the format for height data in vit.xpt and vitr.xpt. Please also include the following variables in the dataset(s):
 - For each height SD score, include reference values (median, SD) using the updated growth charts in the WHO global database.
 - Include variables for growth rates (in SD units) during the pre-study period and the 6- and 12-month periods following the start of treatment. Include variables for the changes in growth rates (SD units) after 6 and 12 months

of treatment relative to the pre-study period.

Please respond as soon as possible via email and also as an official amendment to NDA 22-310.

How quickly do you think you will be able to supply a response to these questions?

Feel free to contact me with any questions or concerns.

Many thanks,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

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

/s/

Jennifer Johnson
9/18/2008 03:41:04 PM
CSO

Submitted September 17, 2008



CASODEX® (bicalutamide) Tablets

NDA 22-310

Module 1.9.1 Amendment to Request for Waiver of Pediatric Studies



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1. REQUEST FOR FULL WAIVER FOR FURTHER PEDIATRIC STUDIES

Product Name: CASODEX (bicalutamide)

NDA Number: 22-310

Sponsor: AstraZeneca Pharmaceuticals LP

Proposed/investigated Indication(s): Testotoxicosis (also known as familial male-limited precocious puberty; FMPP)

Age ranges requested in full waiver: Children – 0 years up to 16 years

Statutory reason(s) for requesting a waiver: Under section 505B(a)(4)(A)(i) of the Act, AstraZeneca requests a full waiver of the requirement to submit further pediatric assessments because “necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed).” Previously AstraZeneca had requested the limited age ranges from 2 years –12 years due to the Written Request containing that age range. This amendment extends the age ranges requested to encompass the full age range.

Applicant Certification/Justification for the waiver: Having to monitor and gather retrospective data to be able to confirm the diagnosis of testotoxicosis prior to start of study treatment would exclude boys prior to 2 years of age, since monitoring would have to start between 0 -1 year of age to diagnosis that the bone age of the patient was at least one year more than the patient’s chronologic age. Also, boys normally reach natural puberty by the age of 13; therefore, boys over the age of 12 are excluded from being study treatment.

Testotoxicosis is an extremely rare disease. The only known public information that documents the prevalence of the disease is available on Orphanet* (http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=3000). Orphanet classifies the prevalence of testotoxicosis at 1-9 boys per 1,000,000. Because of the rarity of testotoxicosis occurrence, it is highly impractical to conduct a sufficient clinical study in this patient population.

* *Orphanet* is a database of information on rare diseases and orphan drugs for all publics. Its aim is to contribute to the improvement of the diagnosis, care and treatment of patients with rare diseases. *Orphanet* includes a Professional Encyclopaedia, which is expert-authored and peer-reviewed, a Patient Encyclopaedia and a Directory of expert Services. This Directory includes information on relevant clinics, clinical laboratories, research activities and patient organisations.

9/3/08



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-310

AstraZeneca Pharmaceuticals LP
Attention: Nicholas J. Troise
Regulatory Affairs Director
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Troise:

Please refer to your new drug application (NDA) dated June 25, 2008, received June 25, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Casodex (bicalutamide) Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is **December 25, 2008**.

During our filing review of your application, we identified the following potential review issues, and request that you submit the following information:

1. method validation report for plasma bicalutamide analysis from _____ (method used for D6873C00003 study at _____),
2. method validation report for plasma bicalutamide analysis from AstraZeneca (method used for D6873C00047 study at AstraZeneca),
3. method validation report for plasma anastrozole analysis from _____ (method used for D6873C00002 study at _____),
4. method validation report for plasma anastrozole analysis from AstraZeneca (method used for D6873C00047 study at AstraZeneca),
5. method validation report for serum estradiol analysis from T
6. study sample analysis report for both bicalutamide and anastrozole from AstraZeneca for D6873C00047 study, and
7. study sample analysis report for serum estradiol analysis from T

b(4)

NDA 22-310

Page 2

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients ages 2-12 years. Please submit information that addresses the pediatric population ages 0-1 years and 13-16 years.

If you have any questions, call Jennifer Johnson, Regulatory Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Mary Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Mary Parks
9/3/2008 02:29:29 PM

Johnson, Jennifer

From: Johnson, Jennifer
Sent: Tuesday, August 12, 2008 2:59 PM
To: 'Valas, E Jane'
Cc: Troise, Nicholas J
Subject: Review Team Questions: NDA 22-310 (Casodex)

Good afternoon Jane,

We are currently reviewing the pediatric NDA 22-310 for Casodex, and have the following clinical and statistical (data clarification and additional electronic data) information requests for Study D6873C00047:

Clinical

According to the inclusion criterion # 3 of the Study D6873C00047 clinical protocol, patients had to have a diagnosis of testotoxicosis based on the following:

- clinical features (progressive sexual precocity documented by Tanner staging and evidence of symmetrical testicular enlargement, and bone age advanced at least > 12 months over chronological age)
- pubertal levels of serum testosterone
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- lack of an increase in serum gonadotropin levels following GnRH stimulation
- exclusion of other causes of precocious puberty (normal plasma beta-human chorionic gonadotropin, normal 17-hydroxyprogesterone, normal levels of dehydroepiandrosterone sulphate).

According to pages 2 and 3 of the CRF, these criteria were to be met at Visit 1 and the following statement was included on Page 3 of the CRF: "If No to any Inclusion criteria, please withdraw Subject and fill in TERM, Withdrawal Section".

Please explain why the following patients were enrolled in the trial given the following:

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- Patient E0009001 had a maximum stimulated LH level > 4 U/L (4.1 U/L) at baseline (Appendix 12.2.8.11) and an elevated 17-OH progesterone of 2.70 nmol/L at baseline (repeat 2.40 nmol/L on Day 1) (Appendix 12.2.8.10 Listing of sex hormones (II)).
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Statistical

1. Pre-study height data for patients E0054003 and E0054004 (twins) were collected on 12/09/04 and 10/18/06. These dates were 871 and 193 days prior to Visit 1 (baseline). The 12/9/04 data were used to compute pre-study growth rates although the 10/18/06 data were the most recent pre-study height data

8/12/2008

measured at least six months prior to the start of the study. Why were the 10/18/06 data not used to calculate the pre-study growth rates for these two patients?

2. Please submit SAS transport dataset(s) with height SD scores. The format should be similar to the format for height data in vit.xpt and vitr.xpt. Please also include the following variables in the dataset(s):
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 - Include variables for growth rates (in SD units) during the pre-study period and the 6- and 12-month periods following the start of treatment. Include variables for the changes in growth rates (SD units) after 6 and 12 months of treatment relative to the pre-study period.

Please respond as soon as possible via email and also as an official amendment to NDA 22-310.

How quickly do you think you will be able to supply a response to these questions?

Feel free to contact me with any questions or concerns.

Many thanks,
Jennifer

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food & Drug Administration
301-796-2194 phone
301-796-9712 fax
jennifer.johnson@fda.hhs.gov

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this page is the manifestation of the electronic signature.**

/s/

Jennifer Johnson

8/12/2008 03:03:19 PM

CSO

Clinical and Statistical Information Requests sent via email to
sponsor

Submitted June 25, 2008



CASODEX® (bicalutamide) Tablets
NDA 22-310

Request for Waiver of Pediatric Studies



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I.	REQUEST FOR FULL WAIVER FOR FURTHER PEDIATRIC STUDIES	3

1. REQUEST FOR FULL WAIVER FOR FURTHER PEDIATRIC STUDIES

Product Name: CASODEX (bicalutamide)

NDA Number: 22-310

Sponsor: AstraZeneca Pharmaceuticals LP

Proposed/investigated Indication(s): Testotoxicosis (also known as familial male-limited precocious puberty; FMPP)

Age ranges requested in full waiver: Children - 2 years up to 12 years

Statutory reason(s) for requesting a waiver: Under section 505B(a)(4)(A)(i) of the Act, AstraZeneca requests a full waiver of the requirement to submit further pediatric assessments because “necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed).”

Applicant Certification/Justification for the waiver: Testotoxicosis is an extremely rare disease. The only known public information that documents the prevalence of the disease is available on Orphanet* (http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=3000). Orphanet classifies the prevalence of testotoxicosis at 1-9 boys per 1,000,000. Because of the rarity of testotoxicosis occurrence, it is highly impractical to conduct a sufficient clinical study in this patient population.

* *Orphanet* is a database of information on rare diseases and orphan drugs for all publics. Its aim is to contribute to the improvement of the diagnosis, care and treatment of patients with rare diseases. *Orphanet* includes a Professional Encyclopaedia, which is expert-authored and peer-reviewed, a Patient Encyclopaedia and a Directory of expert Services. This Directory includes information on relevant clinics, clinical laboratories, research activities and patient organisations.

orphanet

The portal for rare diseases and orphan drugs

[Homepage](#) [Rare diseases](#) [Search](#)

Languages :

Testotoxicosis

Orpha number	ORPHA3000	Synonym(s) Precocious puberty, male limited Sexual precocity, familial, gonadotropin-independent, male-limited
Prevalence	1-9 / 1 000 000	
Inheritance	Autosomal dominant	
Age of onset	Childhood	
ICD 10 code	E30.1	
MIM number	<u>176410</u>	

SUMMARY

Familial, gonadotropin-independent, male-limited sexual precocity is a rare affection leading to precocious signs of puberty in boys (between 2 and 5 years of age). Patients display increased testosterone secretion but decreased secretion of gonadotropins, even after stimulation with luteinizing hormone-releasing hormone (LHRH). The condition may be sporadic or transmitted as a dominant trait; its expression is limited to males. The diagnosis excludes the other causes of precocious puberty with low levels of gonadotropins (adrenal tumors, testicular Leydig cell tumors, adrenal enzymatic blocks, human chorionic gonadotropin (HCG)-secreting tumors, occult intake of androgens). The diagnosis is confirmed by the discovery of a specific mutation activating the LH receptor. Treatment consists of reducing hyperandrogenism in children (sexual maturation, stature), with ketoconazole or a combination of spironolactone/aromatase inhibitors. *Author: Prof. J.C. Carel (February 2005)*.

- [Clinical signs \(6\) \[+\]](#)

- [English](#)
- [Español](#)
- [Deutsch](#)
- [Italiano](#)

• f



CASODEX® (bicalutamide) Tablets

NDA 22-310

1.9.3 – Request for Pediatric Exclusivity Determination

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1. REQUEST FOR PEDIATRIC EXCLUSIVITY DETERMINATION

In accordance with Sections 505A(d)(2) and (3) of the Federal Food, Drug, and Cosmetic Act, AstraZeneca submitted this New Drug Application (NDA) to file the reports of studies associated with the Pediatric Written Request (WR) for CASODEX. The purpose of this NDA is to demonstrate that AstraZeneca has fairly responded to the Written Request and qualify to receive a 6-month pediatric exclusivity.

With this NDA, AstraZeneca requests Pediatric Exclusivity Determination for CASODEX. As suggested in the "Guidance for Industry – Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act" (revised, September 1999), AstraZeneca faxed, on the day of NDA submission, a copy of the NDA cover letter to the Office of Generic Drugs.

To support the review process by FDA, AstraZeneca is providing an Annotated Written Request table (see Section 1.9.3 Annotated Written Request). This table was requested by the Division of Metabolism and Endocrinology Products and provides detailed information on how AstraZeneca fully complied with each item supplied in the Written Request for CASODEX. Furthermore, AstraZeneca has provided in Section 1.9.6 summary of relevant FDA interactions and correspondence regarding pediatric exclusivity along with the current WR and all previous versions of the WR.



Date: 12 June 2008

US Food and Drug Administration (75060099)
Wachovia Bank
Attn: Food and Drug Administration, Lockbox 70963
West WT Harris Blvd, Room NC0810
Charlotte, NC 28262

RE: NDA 22-310
CASODEX® (bicalutamide) tablets
Prescription Drug User Fee Payment: User Fee I.D. No. PD3008439

Dear Madam/Sir:

In accordance with section 736 of the Federal Food, Drug and Cosmetic Act, AstraZeneca Pharmaceuticals LP (AstraZeneca) is providing a Prescription User Fee payment for a NDA for the use of CASODEX.

The User Fee payment is made in the amount of \$1,178,000 and represents the total NDA application fee for fiscal year 2008. A copy of the User Fee Cover Sheet, Form FDA 3397, is enclosed.

Please direct any questions or requests for additional information to me, or in my absence, to Dr. E. Jane Valas, Regulatory Affairs, at (302) 886-2122.

Sincerely,

A handwritten signature in black ink, appearing to read "N. Troise".

Nicholas J. Troise, Director
Regulatory Affairs
Telephone: (302) 886-8016
Fax: (302) 886-2822

NJT/MF

Enclosure

Form FDA 3397 – User Fee Cover Sheet
User Fee Check No. 1500197819

Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See instructions for OMB Statement, below.					
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		PREScription DRUG USER FEE COVERSHEET			
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm .					
1. APPLICANT'S NAME AND ADDRESS ASTRAZENECA PHARMACEUTICALS LP Nicholas Troise 1800 Concord Pike C1C-123A Wilmington DE 19803 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 22-310	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:			
2. TELEPHONE NUMBER 302-8868016	3. PRODUCT NAME CASODEX (bicalutamide)	6. USER FEE I.D. NUMBER PD3008439			
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY					
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO					
<p>OMB Statement: Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <table border="0"> <tr> <td>Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448</td> <td>Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852</td> <td>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</td> </tr> </table>			Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.			
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE <i>Nicholas Troise</i>	TITLE <i>Director</i>	DATE <i>June 12, 2008</i>			
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$1,178,000.00					
Form FDA 3397 (03/07)					

[Close](#) [Print Cover sheet](#)

AstraZeneca

AstraZeneca LP
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

1500197819

FOOD AND DRUG ADMIN
PO Box 70963
CHARLOTTE NC 28272-0963

Payment No.: 500205989
Payment Date: 06/10/2008
Vendor No.: 30002905

Page: 1 of 1

Invoice Number	Invoice Date	Document Number Text	Gross Amount	Discount	Net Amount
AZIE100921	06/10/2008	510635875 <i>User Fee payment for CASODEX (Peds)</i>	1,178,000.00	0.00	1,178,000.00
		Check Total.....			\$1,178,000.00

ANY QUESTIONS REGARDING THIS PAYMENT - CALL (800) 773-7119

AstraZeneca

AstraZeneca LP
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

30002905 4315

1500197819

June 10, 2008

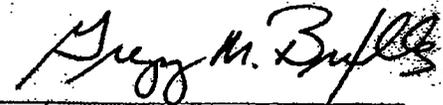
PAY ONE MILLION ONE HUNDRED SEVENTY-EIGHT THOUSAND and 00/100 Dollars

TO THE
ORDER
OF

FOOD AND DRUG ADMIN
PO Box 70963
CHARLOTTE NC 28272-0963

\$ *****1,178,000.00

Bank of America Controlled Disbursement
Bank of America, N.A.
Atlanta, DeKalb County, Georgia
64-1278/611



AUTHORIZED SIGNATURE

PD # 3008439

VOID AFTER 180 DAYS

THIS PAYMENT IS VALID ONLY IF THE ASTRAZENECA LOGO PRINTED IN WHITE INK IN MULTIPLE POSITIONS IS HELD AT AN ANGLE TO VIEW. VOID IF NOT PRESENT.

1500197819 061112788 329 911 2484

1/22/08



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 61,238

AstraZeneca Pharmaceuticals LP
Attention: Jennifer Pavillard
Associate Director, Regulatory Affairs
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Pavillard:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Casodex (bicalutamide) Tablets.

We also refer to your amendment dated September 26, 2007, containing a request for a Pre-NDA meeting to discuss the content and format of the NDA supporting your response to the Casodex Pediatric Written Request. Our October 10, 2007, denial letter indicated that we would provide written responses to your questions in lieu of a formal meeting. We further refer to your submission dated October 31, 2007, which provided the informational package associated with your Pre-NDA meeting request.

Your questions are repeated below and our responses follow in bold print.

Type of NDA

Question 1:

Does the Agency agree that the NDA should be filed as Type 6 NDA with proposed labeling changes presented in the labeling content and format described in 21 CFR 201.56(d) and 201.57?

Yes, this is correct.

Content and Format of the NDA Submission

Question 2:

Does FDA agree that the submission components as detailed in this draft Table of Contents will be sufficient to accept for filing this eCTD NDA?

Clinical: The proposed content and format of the NDA submission are acceptable for submission.

Chemistry, Manufacturing and Controls: In addition to the drug product information listed in your informational package, your NDA should also cross-reference the drug product in the Casodex and Arimidex NDA's since the approved tablets were used to produce the compounded oral suspension. Information should also be provided in the pharmaceutical development for the bicalutamide and anastrozole dispersible tablets.

Pharmacology/Toxicology: The general nonclinical information can be cross-referenced in the NDA submission provided a right of reference to the prior approved NDAs is also provided. However, specific information and studies supporting safety of the pediatric indication should be included rather than referenced in the NDA submission.

Proposed Labeling Changes

Question 3:

Does the Agency agree that both the Casodex and Arimidex labels should be updated with the data obtained from the testotoxicosis pediatric trial (Study D6873C00047)?

We remind you that under PREA and BPCA, if a study does or does not demonstrate safety or efficacy in pediatric populations, even if study results are inconclusive, the label must include information on the study along with a statement of the Secretary's determination.

We cannot agree to this at this time but will consider this question with the appropriate review team during the review of your NDA for Casodex.

Nonclinical Information Cross-Referenced

Question 4:

Does the Agency agree that cross-references to the nonclinical pharmacology, pharmacokinetics, and toxicology reports filed to Casodex NDA 20-498 and Arimidex 20-541 will be sufficient for Module sections of 2.6.2, 2.6.3, 2.6.4, 2.6.5, 4.2.1, 4.2.2, and 4.2.3 (with the exception of Study 0514GR) of the Casodex Pediatric NDA?

The general nonclinical information can be cross-referenced in the NDA submission provided a right of reference to the prior approved NDAs is also provided. However, specific information and studies supporting safety of the pediatric indication should be included rather than referenced in the NDA submission.

Clinical Information

Question 5:

Does the Agency agree that the Efficacy Evaluation and Safety Evaluation sections within the CSR for Study D6873C00047 will suffice as the ISE, ISS, Summary of Clinical Efficacy, and Summary of Clinical Safety and, therefore, grant a waiver for these documents?

Yes.

Statistical Analysis Plan

Question 6:

Does the Agency agree with the statistical approach to the analysis of data for Study D6873C00047 as outlined in the SAP dated September 2007?

The Statistical Analysis Plan is acceptable.

Question 7:

Does the Agency agree with replacing the old growth chart with the updated growth charts on the WHO global database?

Your proposal is acceptable. Please present height data both as centimeters (cm) and as standard deviation score (SDS).

Datasets

Question 8:

Does the Agency agree that the content, format, and structure of the datasets as provided and described will be adequate for review of the NDA?

The proposed datasets are acceptable. Additional datasets and information may be requested during the NDA review cycle. Also, provide for the medical reviewer a clear, "plain English" description of the variables included in each dataset.

Tables, Figures and Listings

Question 9:

Does the Agency find the format and content of the proposed Tables and Listings acceptable for review of the NDA?

The proposed Tables and Listings are acceptable. Additional information may be requested during the NDA review cycle.

Outstanding Business

Question 10:

AstraZeneca respectfully requests an update on when we may receive a response to our request the pediatric WR for Casodex?

We anticipate issuing a response by the end of January 2008.

Additional requests:

- A. In order to aid the review for the exclusivity determination provide a table with two columns: in the left column include, sentence by sentence, the most recent version of the Written Request; in the right column include and/or refer to the specific information in the NDA that demonstrates that the requests formulated in the WR have been met (the information in the right column can be hyperlinked to the specific information in the NDA).

B. For your future NDA submission based on Study D6873C00047, you should justify the use of the unapproved dosage strength of 0.5 mg anastrozole oral dispersible tablets as well as the use of 12.5 mg and 25 mg bicalutamide oral dispersible tablets used in the clinical study. Such justification may be satisfied via the following:

- **Formulation proportionality between 0.5 mg and 1 mg anastrozole oral dispersible tablets, among 12.5 mg, 25 mg and 50 mg bicalutamide oral dispersible tablets.**
- **Similarity of *in vitro* dissolution profiles between 0.5 mg and 1 mg anastrozole oral dispersible tablets as well as between 12.5 mg and 50 mg and between 25 mg and 50 mg bicalutamide oral dispersible tablets via the f_2 approach.**

If there is any intention to market the extemporaneous compounded liquid, we recommend that the anastrozole liquid suspension and bicalutamide liquid suspension should be compounded and labeled separately. You should have clear and simple instructions on accurate dosing of the extemporaneously compounded liquid suspensions for the pediatric patients.

You must also conduct the population pharmacokinetic analysis of the plasma bicalutamide and anastrozole concentrations from the D6873C00047 study and provide a report.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, please contact Jennifer Johnson, Regulatory Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Linked Applications

Sponsor Name

Drug Name

IND 61238

ASTRAZENECA
PHARMACEUTICALS LP

CASODEX(BICALUTAMIDE)ORALLY
DISINTEGRATG

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

/s/

MARY H PARKS

01/22/2008

9/20/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 61,238

AstraZeneca Pharmaceuticals LP
Attention: Jennifer Pavillard
Regulatory Affairs Manager
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Pavillard:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CASODEX® (bicalutamide) tablets.

We also refer to the teleconference meeting between representatives of your firm and the FDA on August 10, 2006. The purpose of the meeting was to discuss the items contained in your December 5, 2005 briefing document that were not addressed in the Agency's July 3, 2006 denial of your most recent Proposed Pediatric Study Request (PPSR).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jennifer Johnson, Regulatory Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jennifer Johnson
Regulatory Project Manager
Division of Metabolic and Endocrine Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 10, 2006
TIME: 11:00 a.m.-12:00 p.m.
LOCATION: Teleconference
APPLICATION: IND 61,238
DRUG NAME: CASODEX© (bicalutamide) tablets
TYPE OF MEETING: Type C

MEETING CHAIR: Mary Parks, M.D.

MEETING RECORDER: Jennifer Johnson

FDA ATTENDEES:

Division of Metabolic and Endocrine Products

Mary Parks, M.D.	Division Director
Dragos Roman, M.D.	Clinical Reviewer
Kati Johnson	Supervisory Regulatory Project Manager
Jennifer Johnson	Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

AstraZeneca Pharmaceuticals LP

Jennifer Pavillard	Regulatory Affairs Manager
Darci Bertelsen	Regulatory Affairs Director
Les Clarke	Global Regulatory Affairs Director
Robert Timko	Regulatory CMC Director
Thomas Morris, M.D.	Medical Science Director
James Vasselli, M.D.	Associate Director Clinical Research
Jon Armstrong, M.Sc., B.Sc.	Project Statistician
De Phung, B.Sc.	Statistical Science Director
Alison Mackie, M.Sc., B.Sc.	Senior Clinical Pharmacokineticist, Medical Sciences
Jim Murray, Ph.D.	Associate Director, Product Development

BACKGROUND:

AstraZeneca initially submitted a Proposed Pediatric Study Request to the Agency on December 13, 2002, and was issued a Written Request on April 17, 2003. Amendments were subsequently submitted on October 8, 2003, on April 14, 2004, on September 8, 2004 and on November 9, 2004, and all resulted in amended Written Requests. The latest amendment request (#5) was submitted on December 5, 2005 and also included a meeting request to discuss such changes. The meeting request was denied on December 20, 2005; instead, the Agency preferred to respond in writing.

The firm's request for an amended Written Request contained, among other things, the following components:

- 1) Revise the "Age group and number of subjects to be studied" section from "with 12 evaluable patients" to "with up to 12 evaluable patients"
- 2) Revise the timeframe for submitting final study reports of in the Written Request from "on or before March 31, 2008" to "on or before July 31, 2008"
- 3) Request to waive the requirement for demonstration of bioavailability between the oro-dispersible tablets and the extemporaneously compounded liquid formulation (crushed tablets/marketed product)

In the Agency's December 20, 2005 denial letter, though, only the issue pertaining to the number of patients was addressed. The remainder of AstraZeneca's questions contained in the December 5, 2005 briefing document were not answered, as the Agency viewed the other issues as moot. On July 17, 2006, AstraZeneca requested answers to the unaddressed questions from their December 5, 2005 submission. This teleconference was granted in order to discuss these questions and clarify for AstraZeneca the denial decision (see agenda below).

MEETING OBJECTIVES:

AstraZeneca wishes to discuss the following agenda:

1. Discussion of Open Questions from December 5, 2005 submission (listed below)
 - a. Does FDA agree to revise the TIMEFRAME FOR SUBMITTING REPORTS OF THE STUDIES section in the WR from 'on or before March 31, 2008' to 'on or before July 31, 2008'?
 - b. Does FDA find AstraZeneca's suggestion for developing and marketing alternate age-appropriate compounded liquid formulations of currently marketed ARIMIDEX and CASODEX tablets acceptable?
 - c. Given that Studies D6873C00003 and D6873C00002 have demonstrated comparable bioavailability of the oro-dispersible tablets to the marketed formulation AstraZeneca believes it is not necessary to conduct relative bioavailability studies comparing the compounded liquid formulation to the oro-dispersible tablet. Does FDA agree that the proposed compounded liquid formulations do not need to be used in Studies 1, 2 and 3 in the Written Request to grant pediatric exclusivity?
 - d. Does FDA agree to revise and clarify the Written Request, Section DRUG INFORMATION following the Study 3 information to...? (*See December 5, 2005 submission for proposed text changes.*)
2. Request a clarification on FDA decision regarding patient numbers for pediatric written request.

DISCUSSION POINTS:

1. The Agency can reconsider AstraZeneca's requests and amend the WR if at least 12 patients are enrolled. Per a request from the Pediatric Implementation Team (PdIT), please submit a formal new request to the IND for amendment of the Pediatric Written Request.
2. The timeline for final study report submission should be amended to June 30, 2008, in order to allow the Agency sufficient time (i.e., 90 days prior to patent expiration) for review and consideration of Pediatric Exclusivity Designation.
3. Although not required for Pediatric Exclusivity Determination, in order to obtain marketing approval of an extemporaneously compounded liquid formulation for Casodex© and Arimidex© for the treatment of testotoxicosis in children, the compounded liquid formulation must be proven equivalent to the marketed formulation (or the oro-dispersible formulation). If bioequivalence can be demonstrated in vitro (e.g., via equivalent in vitro dissolution profiles to bridge the formulations), a clinical bioequivalence study is not necessary.

DECISIONS (AGREEMENTS) REACHED:

None

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

None

ATTACHMENTS/HANDOUTS:

None

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

/s/

Jennifer Johnson
9/20/2006 05:00:34 PM