CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

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

Administrative Documents

AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19850-5437

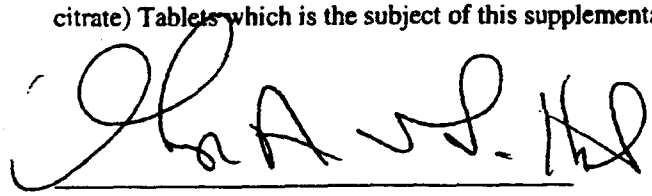
NOLVADEX® (tamoxifen citrate) Tablets
NDA 17-970

Pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act, the information following below is made of record.

A. PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG OR A METHOD OF USING THE DRUG

Certification

Pursuant to 21 CFR Section 314.53(d)(ii),the undersigned certifies that US Patent No. 4,536,516, information relative to which has been submitted previously, claims the formulation, composition and/or method of use of NOLVADEX® (tamoxifen citrate) Tablets which is the subject of this supplemental new drug application.



George A. Gilbert

B. EXCLUSIVITY INFORMATION

1. Exclusivity Claim

AstraZeneca Pharmaceuticals LP claims an exclusivity period of three years for the change in NOLVADEX® (tamoxifen citrate) Tablets presented in this supplemental new drug application.

AstraZeneca Pharmaceuticals LP also claims all applicable six month exclusivity extensions provided under the Pediatric Studies of Drugs provisions of the Food and Drug Administration Modernization Act of 1997.

2. Authority for Exclusivity Claim

Exclusivity for the change in NOLVADEX® (tamoxifen citrate) Tablets presented in this supplemental new drug application is being claimed pursuant to 21 CFR Section 314.108(b)(5).

AstraZeneca Pharmaceuticals LP also claims all applicable six month exclusivity extensions provided under the Pediatric Studies of Drugs provisions of the Food and Drug Administration Modernization Act of 1997

3. Information Demonstrating this Supplemental Application Contains New Clinical Investigations Conducted or Sponsored by the Applicant that are Essential to the Approval of this Supplemental New Drug Application.

a. Certification of New Clinical Investigations

AstraZeneca Pharmaceuticals LP certifies that to the best of its knowledge, each of the clinical investigations included in this supplemental new drug application meets the definition of "new clinical investigation" set forth in 21 CFR Section 314.108(a).

STEPHEN RUBIN, MD

b. Essential to Approval

(i) Literature Search

Attached as Exhibit A is a list of all published studies and publicly available reports of clinical investigations known to AstraZeneca Pharmaceuticals LP through a literature search that are relevant to the conditions for which AstraZeneca Pharmaceuticals LP is seeking approval.

(ii) Certification

AstraZeneca Pharmaceuticals LP certifies that it has thoroughly searched the scientific literature and, to the best of its knowledge, the list of relevant published studies and/or publicly available reports is complete and accurate, and in the opinion of AstraZeneca Pharmaceuticals LP, such published studies and/or publicly available reports do not provide a sufficient basis for the approval of the conditions for which AstraZeneca Pharmaceuticals LP is seeking approval without reference to the new clinical investigation(s) in this supplemental new drug application.

STEPHEN RUBIN, MD

(iii) Explanation

The listed published studies and/or publicly available reports of clinical investigations do not provide sufficient basis for the approval of the conditions for which AstraZeneca Pharmaceuticals LP is seeking approval, without reference to the new clinical investigations in this supplemental new drug application.

The new clinical investigations provide safety and efficacy data regarding use of NOLVADEX® (tamoxifen citrate) Tablets for the treatment of patients with McCune-Albright Syndrome that could not be gleaned from published information. Accordingly, these new clinical investigations are essential to the approval of this supplemental new drug application.

c. Conducted or Sponsored by the Applicant.

AstraZeneca Pharmaceuticals LP is the sponsor named in form FDA-1571 for IND —— under which the new clinical investigations essential to the approval of this supplemental new drug application were conducted..

EXHIBIT A

Nolvadex (tamoxifen citrate) and McCune-Albright Syndrome
Literature Search Conducted: January 11, 2002

1. Eugster EA, Pescovitz OH. **Advances in the treatment of precocious puberty.** Expert Opinion on Investigational Drugs 2001;10(9):1623-30. PLANET-200100288164 Review, 59 Refs, English

2. Eugster EA, Shankar R, Feezle LK, Pescovitz OH. **Tamoxifen Treatment of Progressive Precocious Puberty in a Patient with McCune-Albright Syndrome.** Journal of Pediatric Endocrinology & Metabolism 1999;12(5)(Suppl):681-686. PLANET-199900257225 (MEDLEY-0055775)
Article, Case report, English

   12th National Meeting of the Italian Society for Pediatric Endocrinology and Diabetology (SIEDP), Oct 1999

3. Eugster EA, Shankar R, Feezle LK, Pescovitz OH. **Tamoxifen Treatment of Progressive Precocious Puberty in a Patient With McCune-Albright Syndrome.** Pediatric Research 1998;43(4)(Suppl):74A, Abs 420. PLANET-199800251591 (MEDLEY-0050113)
Case report, Meeting abstract, English

   108th Annual Meeting of The American Pediatric Society and 67th Annual Meeting of Society for Pediatric Research, New Orleans, 1-5 May 1998

4. Lustig LR, Holliday MJ, McCarthy EF, Nager GT. **Fibrous dysplasia involving the skull base and temporal bone.** Archives of Otolaryngology - Head and Neck Surgery 2001;127(10):1239-47. PLANET-200100289755 Article, English
Additional reference in Planet 199900257225

5. Rodens K, Mueller M, Teller WM. **Clinical, hormonal and sonographical characteristics of remission during treatment of pseudoprecocious puberty in the McCune-Albright syndrome. A longitudinal study.** Acta Endocrinologica 1989;120(1):172-173, Abs 186. PLANET-198900230953 (MEDLEY-0028810)
Case report, Meeting abstract, English

   Symposium of the German Society of Endocrinology, Karlsruhe, 22-25 Feb 1989

6. Van Wyk JJ, Smith EP. **Insulin-Like Growth Factors and Skeletal Growth: Possibilities for Therapeutic Interventions. (Review, 59 refs).** Journal of Clinical Endocrinology and Metabolism 1999;84(12):4349-4354. PLANET-199900258783 (MEDLEY-0057107)
Article, Review, 59 Refs, English, minor mention

7. Wudy SA, Rodens K, Homoki J, Teller WM. **Tamoxifen for treatment of sexual precocity in girls with McCune-Albright syndrome.** Pediatric Reviews & Communications. Vol 7(2) (pp 115-120), 1993.

EXCLUSIVITY SUMMARY for NDA # 21-109 SUPPL #

Trade Name Nolvadex Generic Name Tamoxifen citrate tablets

Applicant Name AstraZeneca Pharmaceuticals LP HFD-510

Approval Date August 30, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/X/ (Type 6) NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /X_/

      If yes, what type(SE1, SE2, etc.)?

   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 /X/ 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.

      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:

d) Did the applicant request exclusivity?
Pediatric Exclusivity

YES /_X_/ NO /___/

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

6 months of Pediatric Exclusivity

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

YES /X/ NO / /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /_X/ NO / /

If yes, NDA # 17-970 Drug Name Nolvadex (tamoxifen)

Please note that this application proposes the addition of pediatric study information into the label, but does not provide for a new indication or patient population.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO / _/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 #

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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 /_X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 /_X/ 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 9:**

(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 /_X/

(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:

(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 /X_/

If yes, explain:

(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 # 6157US/0013

Investigation #2, Study #

Investigation #3, Study #

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 /X_/
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:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(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 /___/ NO /X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(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 # ___6157US/0013

Investigation #__, Study #

Investigation #__, Study #

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

[redacted]

support will mean providing 5
the study.

(a) For each investigatio
question 3(c): if the
under an IND, was the
1571 as the sponsor?

Investigation #1

IND # [redacted] YES /_

Investigation #2

IND # _____ YES /___/

(b) For each investigation
for which the applicant
sponsor, did the applic
applicant's predecessor
substantial support for

Investigation #1

YES /___/ Explain _____

_____

_____

Investigation #2

YES /___/ Explain _____

_____

_____

[redacted]

(c) Notwithstanding an answer of "yes" t
there other reasons to believe that
should not be credited with having "
sponsored" the study? (Purchased st
used as the basis for exclusivity.
rights to the drug are purchased (no
the drug), the applicant may be cons
sponsored or conducted the studies s
conducted by its predecessor in inte

YES /___/

If yes, explain: _____

_____

_____

/S/

Monika Johnson, PharmD
Signature of Preparer
Title: Regulatory Project Manager

/S/

David G. Orloff, MD
Signature of Office or Division Director

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

David Orloff
9/11/02 05:32:29 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA# : 21-109 Supplement Type (e.g. SE5): Type 6 Supplement Number:

Stamp Date: February 28, 2002 Action Date: August 30, 2002

HFD 510 Trade and generic names/dosage form: Nolvadex (tamoxifen citrate) 20 mg tablets

Applicant: AstraZeneca Pharmaceuticals, LP Therapeutic Class: 6P

Indication(s) previously approved: Metastatic Breast Cancer, Adjuvant Treatment of Breast Cancer, Ductal Carcinoma In Situ, Reduction in Breast Cancer Incidence in High Risk Women. Please consult NDA 17-970 in the Division of Oncologic Drug Products, HFD-150

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): None. The application provides for revised labeling based on the final study report of a pediatric study. The study was requested in a Written Request for tamoxifen citrate tablets to obtain safety, efficacy and pharmacokinetic information in girls with McCune-Albright Syndrome and progressive precocious puberty.

Indication #1: N/A

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- X No: Please check all that apply: X Partial Waiver ___Deferred X Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- X There are safety concerns, for ages < 2 years old
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- X Other: It is likely that the precocious puberty process is completed when >10 years old

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min	**kg**	**mo.**	**yr.**	**Tanner Stage**	
Max	**kg**	**mo.**	**yr.**	**Tanner Stage**	

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min	**kg 14.1**	**mo.**	**yr. 2.9**	**Tanner Stage over and equal to 2**	
Max	**kg 57.8**	**mo.**	**yr. 10.9**	**Tanner Stage over and equal to 2**	

Comments:

Concurrence from Dr. Dragos Roman, Reviewing Medical Officer September 6, 2002.

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 301-594-7337

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/s/

Monika Johnson
9/11/02 01:41:45 PM
CSO

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA: 04/05/00.
Application Written Request was made to NDA/ #___17-970_____
Timeframe Noted in Written Request for Submission of Studies: 07/31/02.
NDA# _21-109___ Supplement #__000_ Choose one ~~SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR~~ 6P
Sponsor __AstraZeneca Pharmaceuticals, Inc.__
Generic Name __Tamoxifen citrate_____ Trade Name _____Nolvadex_____
Strength_____20 mg_____ Dosage Form/Route _____Tablet_____
Date of Submission of Reports of Studies: 02/28/02.
Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 05/16/02.

Was a formal Written Request made for the pediatric studies submitted?	Y _X_	N ___
Were the studies submitted after the Written Request?	Y _X_	N ___
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y _X_	N ___
Was the timeframe noted in the Written Request for submission of studies met?	Y _X_	N ___
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?	Y _X_	N ___
Did the studies fairly respond to the Written Request?	Y X___	N ___

SIGNED_____ /S/ 5/16/2002 DATE March 16, 2002
(Reviewing Medical Officer)

Do not enter in DFS - FORWARD TO PEDIATRIC EXCLUSIVITY BOARD HFD-960

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
17-970	4536516	8/20/2002

SIGNED _____ /S/ DATE 5/16/02

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/s/

Grace Carmouze
5/17/02 05:24:37 PM

ITEM 16 DEBARMENT CERTIFICATION

16.0 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 supplemental New Drug Application for NOLVADEX™ (tamoxifen citrate), the services of any person in any capacity debarred under section 306 (a) or (b).

Sincerely,

Anthony Rogers, Vice President
Regulatory Affairs
AstraZeneca

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: July 30, 2002

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-109 Nolvadex (tamoxifen citrate)
AstraZeneca

SUBJECT: NDA review issues and recommended action

Background

This Type 6 NDA (essentially an efficacy supplement for an NDA that resides in another division) proposes approval of tamoxifen citrate for the treatment of McCune-Albright syndrome. This is a disorder resulting from a mutation in a G-protein subunit that is leads to a mosaic of hormone-producing tissues possessing constitutive activity. Notable among these tissues is the ovary which in an episodic fashion, beginning at young age, may secrete estrogens in a gonadotropin independent manner, leading to vaginal bleeding, accelerated linear growth and bone-age advancement, and potentially progressing to central precocious puberty, premature epiphyseal closure, and compromise of final height, not to mention the psychosocial ramifications of precocious puberty itself.

Tamoxifen citrate is a non-steroidal antiestrogen (SERM) approved for the treatment of metastatic breast cancer in women and in men and for reduction in risk for breast cancer in women at high risk. Notably, tamoxifen labeling contains a boxed warning regarding the risk of uterine malignancy, both endometrial carcinoma and rare uterine sarcoma, in women treated with the drug. Likewise, the boxed warning addresses the risk of stroke and venous thromboembolism in tamoxifen-treated women.

A written request for pediatric studies was issued for tamoxifen on April 5, 2000. A 1-year, open-label, uncontrolled treatment study in 28 girls with MAS was completed by the sponsor and submitted in the NDA. Pediatric exclusivity has been granted for Nolvadex based on a judgment that the study fairly met the demands of the written request.

Clinical Issues

Efficacy

Drs. Roman and Sahlroot have reviewed the efficacy information. Conclusions regarding effectiveness in blocking the effects of estrogens in MAS are hampered by the fact that baseline data on vaginal bleeding episodes, rate of growth, and of bone age advance were retrospective for some variable period prior to randomization. Additionally, for bone age particularly, there are significant missing baseline data.

Despite this, briefly summarized, tamoxifen therapy was associated with a reduction in vaginal bleeding episodes of an average 50%, with a statistically significant reduction in bone age advance, and with a statistically significant slowing of linear growth relative to pre-study baseline.

Dr. Roman points out that the only treatment failures with regard to linear growth were in the subgroup of patients with bone ages of < 7 years at baseline. This may suggest that the apparent efficacy in this regard was confounded by bone-age-related slowing of growth in those with higher bone ages at trial entry.

Notwithstanding this, Dr. Roman concludes and I concur that improvement in the course of the disease in a subset of patients was likely due to drug. Within the limitations of an open-label, uncontrolled study, it appears that tamoxifen was effective to varying degrees in some of the treated patients. It is clear, however, that the treatment was far from a "cure" for the aspects of the syndrome related to excess estrogen production. These data support the consideration of the use of tamoxifen in girls with MAS.

Safety
There were no serious adverse events in the trial. The most significant safety concern is based on an average doubling of uterine volume during the course of the trial. Though mean uterine volume still remained in the range of normal for age, in light of the known effects of tamoxifen in adults women, the finding in children bears discussion in labeling and directs follow up of patients with MAS treated with tamoxifen.

Labeling
Labeling has been negotiated to include addition of information on efficacy and safety in MAS and to add warning language in several places about the limitations of the safety experience in MAS with particular regard to uterus.

Biopharmaceutics
OCPB finds the PK data from the MAS trial acceptable and adequate to support changes to labeling.

Pharmacology/Toxicology
No new toxicology studies were requested or submitted.

Chemistry/ Microbiology
This is an approved drug.

Establishment Inspections
Acceptable.

Environmental Assessment
Exclusion requested and granted.

DSI/Data Integrity
No site audits were requested or performed.

Financial disclosure
The financial disclosure information is in order. One clinical investigator received significant payments of other sorts of ~~~~ This investigator was a sub-investigator at a site that recruited a single patient. No bias is expected that would have affected trial outcomes.

ODS/DMETS
No issues

Conclusions
The small, open-label study in MAS supports careful use of tamoxifen in this syndrome characterized by autonomous ovarian estrogen secretion and precocious puberty. The principal safety concern relates to the known stimulatory effects of the drug on the uterus and the known long-term risks in adult women of uterine malignancies. Strong balancing warning language has been incorporated into labeling sections that discuss use in MAS.

Recommendation
This application may be approved.

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/s/

David Orloff
7/31/02 06:04:38 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

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).

NOLVADEX 6157US/0013

Please mark the applicable checkbox.

[X] (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	TITLE
Tony Rogers	Exec. Dir; Reg. Affairs
FIRM/ORGANIZATION: AstraZeneca	
SIGNATURE	DATE: 21 Jan 02

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

FORM FDA 3454 (3/99)

Nolvadex - Investigators' Reply to Request for Disclosure — Trial 6157US/0013

No Financial Arrangements

(As of Tuesday – January 15, 2002)

Name	Investigator Type/Center No.	Facility/Department	Address
Dr. Val Abbassi	PI 0001	Georgetown University Medical Center GUH Dept. of Pediatrics	3800 Reservoir Rd NW Washington DC 20007 USA
Dr. David Brown	PI 0003	Minneapolis Children's Medical Center Pediatric Endocrinology and Metabolism	2545 Chicago Avenue So #408 Minneapolis MN 55404 USA
Dr. Gertrude Costin	PI 0005	Childrens Hosp of LA - USC School of Medicine Div of Endocrinology & Metabolism	4650 Sunset Blvd Los Angles CA 90027 USA
	SI 0005		
	SI 0005		
	SI 0005		
	SI 0005		
	SI 0005		
	SI 0005		

Nolvadex - Investigators' Reply to Request for Disclosure — Trial 6157US/0013

No Financial Arrangements

(As of Tuesday – January 15, 2002)

Name	Investigator Type/Center No.	Facility/Department	Address
Dr. Mark M. Danney	PI 0006	University of Texas Health Sciences Cntr, Dept. of Pediatrics	7703 Floyd Curl Drive San Antonio TX 78284 USA
	SI 0006		
Dr. Larry C. Deeb	PI 0007	Children's Clinic Pediatric Endocrinology	2416 East Plaze Drive Tallahassee FL 32308 USA
Dr. Joan R. DiMartino-Nardi	PI 0008	Montefiore Medical Center Pediatric Endocrinology	111 East 210th Street Bronx NY 10467 USA
Dr. Erica A. Eugster	PI 0009	Riley Hosptial for Children - Pediatric Endocrinology Riley A 5984, Indiana Univ. Med Center	702 Barnhill Drive Indianopolis IN 46202 USA
	SI 0009		
	SI 0009		
	SI 0009		
	SI 0009		

Nolvadex - Investigators' Reply to Request for Disclosure

Trial 6157US/0013

No Financial Arrangements

(As of Tuesday – January 15, 2002)

Name	Investigator Type/Center No.	Facility/Department	Address
	SI 0009		
	SI 0009		
	SI 0009		
	SI 0009		
	SI 0009		
	SI 0009		
Dr. Patricia Y. Fechner	PI 0010	Stanford University Medical Center Div of Pediatric Endocrinology	300 Pasture Drive - Rm S-302 Stanford CA 94305 USA
	SI 0010		
	SI 0010		

Nolvadex - Investigators' Reply to Request for Disclosure — Trial 6157US/0013

No Financial Arrangements

(As of Tuesday – January 15, 2002)

Name	Investigator Type/Center No.	Facility/Department	Address
	SI 0010		
	SI 0010		
	SI 0010		
Dr. Nicholas Jospe	PI 0012	Strong Memorial Hospital Dept of Pediatrics Box 777	601 Elmwood Avenue Rochester NY 14642- USA
Dr. Michael S. Kappy	PI 0013	The Children's Hospital Cheif, Pediatric Endocrinology	1056 E. 19th Avenue - B-265 Denver CO 80218- USA
	SI 0013		
Dr. Ann K. Kershnar	PI 0014	Southern CA Permanente MedicalGroup. Suite 307	9449 E. Imperial Hwy Downey CA 90242 USA
Dr. Michael A. Levine	PI 0015	Johns Hopkins Hospital Pediatric Endocrinology	600 N. Wolfe Street - Park Bldg Rm# 211 Baltimore MD 21287 USA
	SI 0015		
Dr. Catherine Mao	PI 0016	Harbor UCLA Medical Center	1124 W. Carson Street Torrance CA 90502- USA
Dr. Robert McVie	PI 0017	LSU-MC Dept of Pediatrics	1501 Kings Hwy. - PO Box 33932 Shreveport LA 71130- USA
	SI 0017		
Dr. Thomas Moshang, Jr	PI 0018	The Children's Hospital of Philadelphia	34th & Civic Center Blvd Philadelphia PA 19104- USA

Nolvadex - Investigators' Reply to Request for Disclosure — Trial 6157US/0013

No Financial Arrangements

(As of Tuesday – January 15, 2002)

Name	Investigator Type/Center No.	Facility/Department	Address
	SI 0018		
	SI 0018		
	SI 0018		
	SI 0018		
	SI 0018		
	SI 0018		
Dr. Susan B. Nuncz	PI 0020	Children's National Medical Center	111 Michigan Ave Washington DC 20010- USA
Dr. Jerry S. Olshan	PI 0021	Maine Pediatric Specialtiy Group	295 Forest Avenue Portland ME 04101- USA
Dr. Robert A. Richman	PI 0023	SUNY Health Science Center Pediatric Endocrine Center	750 East Adams Street Syracuse NY 13210- USA
Dr. Enriquc R. Martincz	PI 0025		
Dr. Janine E. Sanchez	PI 0026	Mailman Center for Child Development	1601 NW 12th Ave Room 3044A Miami FL 33136- USA
Dr. Malcolm S. Schwartz	PI 0027	The Children's Mercy Hospital Pediatric Endocrinology	2401 Gillham Road Kansas City MO 64108- USA
Dr. Wayne Moore	PI 0028	The Children's Mercy Hospital Pediatric Endocrinology	2401 Gillham Road Kansas City MO 64108- USA

APPEARS THIS WAY ON ORIGINAL

Nolvadex - Investigators' Reply to Request for Disclosure

Trial 6157US/0013

No Financial Arrangements

(As of Tuesday – January 15, 2002)

Name	Investigator Type/Center No.	Facility/Department	Address
Dr. I. David Schwartz	PI 0028	The Children's Mercy Hospital Pediatric Endocrinology	2401 Gillham Road Kansas City MO 64108- USA
	SI 0028		
	SI 0028		
	SI 0028		
Dr. Paulo Solberg	PI 0029	Duke University Medical Center Division of Pediatric Endocrinology	Box 30-80 Durham NC 27710 USA
Dr. Norman P. Spack	PI 0030	The Children's Hospital Endocrine Division	300 Longwood Avenue Boston MA 02115- USA
Dr. Dennis M. Styne MD	PI 0031	UC Davis Medical Center Dept of Pediatrics	2516 Stockton Blvd Ticon II Sacramento CA 95817 USA
	SI 0031		
Dr. David Finegold	PI 0033	Childrens Hospital of Pittsburg	3705 Fifth Ave at DeSoto Pittsburg PA 15312- USA
	SI 0033 0045		
	SI 0047		
	SI 0047		

Nolvadex - Investigators' Reply to Request for Disclosure

Trial 6157US/0013

No Financial Arrangements

(As of Tuesday – January 15, 2002)

Name	Investigator Type/Center No.	Facility/Department	Address
Dr. Bernard L. Silverman	PI 0049	Children's Memorial Hospital	2300 Children's Place Box 54 Chicago IL 60614- USA
Dr. Ivan Zador MD	PI 0051	Pediatric Endocrinology	1000 North Oak Ave - 1A4 Marshfield WI 54449 USA
Dr. Kenneth R. Rettig MD	PI 0052	USA Childrens Specialty Center Suite 1430	1504 Spring Hill Ave Mobile AL 36640 USA

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Nolvadex - Investigator Request for Disclosure

No Response to Request – Did Not Participate

(As of Tuesday – January 15, 2002)

Trial No. 6157US/0013

Name	Investigator Type/Center No.	Facility/Department	Address
Dr. Ramin Alemzadeh	PI 0002	Medical College of Wisconsin-MACC Fund Res Cntr Division of Pediatric Endo & Metob	8701 Watertown Plank Road Milwaukee WI 53226 USA
Dr. Kevin Corley	PI 0004		985450 Nebraska Medical Center Omaha NE 68198 USA
	SI 0017		
	SI 0021		
Dr. David R. Repaske PhD	PI 0022	Children's Hospital Medical Center Division of Endocrinology	3333 Burnet Avenue Cincinnati OH 45229 USA
Dr. Susan R. Rose	PI 0024	University of Tennessee, Memphis Professor of Pediatrics	50 N. Dunlap, 4th Floor Memphis TN 38103- USA
	SI 0029		
Dr. Christine Temand MD	PI 0032	13-124 PWB	420 Delaware St SE Minneapolis MN 55455 USA
	SI 0032		
	SI 0032		
	SI 0032		
	SI 0032		
	SI 0032		

APPEARS THIS WAY ON ORIGINAL

5

Nolvadex - Investigator Request for Disclosure

No Response to Request – Did Not Participate

(As of Tuesday – January 15, 2002)

Trial No. 6157US/0013

Name	Investigator Type/Center No.	Facility/Department	Address
	SI 0032		
	SI 0032		
Dr. Paul Boepple	PI 0035	Massachusetts General Hospital Reproductive Encocrine Unit	Fruit Street - Bartlett Hall Ext. 511 Boston MA 02114- USA
Dr. Rosalind S. Brown	PI 0036	U Mass Memorial Health Care Dept of Pediatrics	55 Lake Ave North Worcester MA 01655- USA
Dr. Leona Cuttler	PI 0047	Rainbow Babies and Children's Hospital Case Western Reserve Univ	11100 Euclid Avenue - Room 737 Cleveland OH 44106 USA
	SI 0049		
Dr. Stephen H. LaFranchi	PI 0053	Oregon Health Sciences Univ Dept of Pediatrics (CDW-5)	3161 SW Sam Jackson Park Rd Portland OR 97201 USA
	SI 0053		
	SI 0053		
	SI 0053		
Dr. Celine Huot MD	PI 0054	Hopital Sainte-Justine Endocrinology	3175 Cote Sainte-Catherine Montreal Quebec H3T 1C5 Canada
	SI 0054		
	SI 0054		

5

Nolvadex - Investigator Request for Disclosure

Trial No. 6157US/0013

No Response to Request – Did Not Participate

(As of Tuesday – January 15, 2002)

Name	Investigator Type/Center No.	Facility/Department	Address
	SI 0054		
	SI 0054		
	SI 0054		

Department of Health and Human Services
Public Health Service
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

TO BE COMPLETED BY APPLICANT

The following information concerning ___Dr. ___ _____, who participated
Name of clinical investigator

as a clinical investigator in the submitted study ___Nolvadex 6157US/0013___ is
Name of clinical study

submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest in the sponsor of the covered study held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME		TITLE
Tony Rogers	for APR	Exec. Dir. Reg. Affairs
FIRM/ORGANIZATION		
AstraZeneca		
SIGNATURE		DATE
		21 Jan 02

Paperwork Reduction Act Statement

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

Nolvadex - Investigators' Reply to Request for Disclosure

Trial 6157US/0013

Disclosure Statement Received

(As of Tuesday – January 15, 2002)

Name	Investigator Type/Center No.	Facility/Department/ Address	Disclosure Statement
	SI 0009		

AstraZeneca

Memo

To:

From: Jean Fennimore, CRM

CC:

Date: 1/21/2002

Re: Dr. [redacted] Financial Disclosure

Dr. [redacted] completed a disclosure statement as notification that [redacted] received a sum greater than [redacted] from AstraZeneca, LP.

Dr. [redacted] was consulted as a Pediatric Endocrinologist and has provided AstraZeneca with a clinical perspective which was necessary for developing a protocol specific to this pediatric endocrine disorder.

Dr. [redacted] served as a Sub-Investigator for one of the Clinical Investigative sites in the Nolvadex Trial 6157US/0013. This site enrolled one patient into the trial and was recruited by the Principal Investigator, thus there was no bias that would affect the outcome of the trial.

APPEARS THIS WAY
ON ORIGINAL

NDA 21-109

NO ADVERTISING

NDA 21-109

The Safety Update Information is included in the Medical Officer review dated July 23, 2002

NDA 21-109

NO DSI AUDITS

NDA REGULATORY FILING REVIEW

NDA 21-109, Nolvadex, Tamoxifen tablets 20 mg

Applicant: AstraZeneca Pharmaceuticals LP
Date of Application: February 28, 2002
Date of Receipt: March 1, 2002
Date of Filing Meeting: March 20, 2002
Filing Date: April 30, 2002

Indication(s) requested: No apparent pediatric indication. Firm wants to includes the pediatric clinical studies, adverse reactions, pediatric use sections in the label.

Type of Application: Full NDA _____ Supplement __
Type 6 (parent NDA 17-970 in HFD-150 Division of Oncology Drug Products)
(b)(1) _____ (b)(2) _____

Therapeutic Classifications: 6P, Priority
Resubmission after a withdrawal or refuse to file __No_____
Chemical Classification: (1,2,3 etc.)_____
Other (orphan, OTC, etc.)_____

User Fee Status: Paid (1/2 fee, clinical data required)_____ Waived (e.g., small business, public health) _____ Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES___XX____ NO_____
User Fee ID#_____4304_____
Clinical data? YES __XX_____ NO _____ Referenced to _____
Date clock started after UN _____N/A_____

User Fee Goal date: _September 1, 2002_____

Action Goal Date (optional) ___July 26, 2002_____

- Does the submission contain an accurate comprehensive index? YES
- Form 356h included with authorized signature? YES
- Submission complete as required under 21 CFR 314.50? YES
- If electronic NDA, does it follow the Guidance? YES
- Patent information included with authorized signature? YES

Exclusivity requested? Not requested implicitly, rather this NDA is a response to a Written Request (WR) which, if satisfactory, will convey 6 months of exclusivity.

- Correctly worded Debarment Certification included with authorized signature? YES

Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. 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 the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ..."

- Financial Disclosure included with authorized signature? YES
  (Forms 3454 and/or 3455)

Note: one investigator with interest (3455), however because this investigator only enrolled one patients, it was deemed non-influencial in overall results of the study.

- Pediatric Rule appears to be addressed for all indications? Response to a WR, N/A
- Pediatric assessment of all ages? N/A
  (If multiple indications, answer for each indication.)
  If NO, for what ages was a waiver requested? _____
  For what ages was a deferral requested? _____

- Field Copy Certification (that it is a true copy of the CMC technical section)? NO
  Note: Nolvadex is an approved product, this document is not in the application.

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES

Drug name/Applicant name correct in COMIS? YES

List referenced IND numbers: [redacted] (Written Request)

End-of-Phase 2 Meeting? NO
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? NO

Project Management

Copy of the labeling (PI) sent to DDMAC? YES

Trade name and labeling (PI) sent to ODS? NO
(Trade name not changing)

Advisory Committee Meeting needed? NO
Note: Pediatric Exclusivity Board Meeting will take place May 16, 2002

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? NO

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES

  If no, did sponsor submit a complete environmental assessment?

- EA consulted to Nancy Sager (HFD-357)? NO

- Establishment Evaluation Request (EER) package submitted? YES

- Parenteral Applications Consulted to Sterile Products (HFD-805)? N/A

505(b)(2) **NA___XXX_____**

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)?
Yes ____ No _____
(Normally, FDA will refuse-to-file such applications.)

Is 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)?
Yes _____ No _____
If yes, the application must be refused for filing under 314.54(b)(1)

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?
Yes _____ No _____
If yes, the application must be refused for filing under 314.54(b)(2)

For a 505(b)(2) application, which of the following does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): **No relevant patents.**

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the **applicant:**

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

- Submit a statement as to whether the listed drug(s) identified have received a period of marketing exclusivity?

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

If the application is a 505(b)(2), has the Director, Div. of Regulatory Policy II, HFD-007 been notified? YES _____ NO _____

ATTACHMENT

FILING MEETING MINUTES

DATE: March 20, 2002

BACKGROUND
Nolvadex (tamoxifen citrate) tablets are approved for treatment of Metastatic Breast Cancer, Adjuvant Treatment of Breast Cancer, Ductal Carcinoma in Situ, and Reduction in Breast Cancer Incidence in High Risk Women. The February 28, 2002, submission is the pediatric study report using tamoxifen citrate tablets for treatment of McCune Albright Syndrome which is in response to a Written Request issued by Division of Metabolic and Endocrine Drug Products (DMEDP) August 4, 2000.

NDA 21-109 (type 6 efficacy supplement) was created in DMEDP for administrative purposes as the parent NDA resides in the Division of Oncology.

ATTENDEES:

Dragos Roman, M.D.	Medical Officer
Hae Young Ahn, PhD	Biopharmaceutics Team Leader
Xiaoxiong (Jim) Wei, PhD	Biopharmaceutics Reviewer
Jon (Todd) Sahlroot, PhD	Statistician Team Leader/Reviewer
Enid Galliers	Chief Project Management
Monika Johnson, PharmD	Regulatory Project Manager

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Dragos Roman, MD
Secondary Medical:	
Statistical:	Jon (Todd) Sahlroot, PhD
Pharmacology:	Jeri El Hage
Statistical Pharmacology:	
Chemist:	Yvonne Yang, PhD
Environmental Assessment (if needed):	Yvonne Yang, PhD
Biopharmaceutical:	Jim Wei, PhD
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Project Manager:	Monika Johnson, PharmD
Other Consults:	

Is the application affected by the application integrity policy (AIP) NO

Per reviewers, all parts in English, or English translation? N/A

CLINICAL – File ___XXX_____ Refuse to file _____

- Clinical site inspection needed: YES_____ NO__XXX_____

MICROBIOLOGY CLINICAL – File_____N/A_____ Refuse to file_____

STATISTICAL – File ___XXX_____ Refuse to file _____

BIOPHARMACEUTICS – File ___XXX_____ Refuse to file _____

- Biopharm. inspection Needed: YES_____ NO __XXX_____

PHARMACOLOGY – File ___XXX_____ Refuse to file _____

CHEMISTRY –

- Establishment ready for inspection? YES__XX___NO_____ File_XX____ Refuse to file _____

REGULATORY CONCLUSIONS/DEFICIENCIES:

_XX_____The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ The application is unsuitable for filing. Explain why:

__Monika Johnson, PharmD
Project Manager, HFD-510

79 pages redacted from this section of the approval package consisted of draft labeling

MEMORANDUM

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

DATE: March 21, 2002

TO: IND File IND [redacted]

FROM: Enid Galliers, CPMS, DMEDP

SUBJECT: **Pending request to amend a Written Request (PB)**
S/N-006 letter date 27-JUN-2001
IND [redacted] Nolvadex (tamoxifen citrate) tablets

AstraZeneca requested an amendment to the issued WR. While the pediatric action package containing an amended written request was circulating, the firm submitted the pediatric data in a type 6 NDA (NDA 21-109). Because it is too late for an amended WR to affect an already submitted NDA or supplement, the Agency considers the pending PB to be withdrawn effective on the date that NDA 21-109 was received, March 1, 2002.

INSTRUCTIONS TO DDR-510 for COMIS ENTRY:

Close S/N-006 PB with a decision "WITHDRAW" dated 01-MAR-2002.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

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
1800 Concord Pike
PO Box 8355
Wilmington, DE 19850-8355

2. TELEPHONE NUMBER *(Include Area Code)*

(302-886-7533) Laura Garcia-Davenport, MS

3. PRODUCT NAME
Nolvadex™ (tamoxifen citrate)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
21-109/S-000

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ 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:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

____ (APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER
4304

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See Item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetics Act
(See Item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See Item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?
☐ YES ☒ NO
(See Item 8, reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Laura Garcia-Davenport, MS	Associate Regulatory Affairs Director	FEB 2 1 2002

FORM FDA 3397 (4/01)

Created by Regulatory Systems Management: ALP

PM: Johnson, P
Cost $156,660
on Feb 28, 20

USER FEE VALIDATION SHEET

Type 6 NDA

NDA # 21-109 Supp. Type & # N-000 UFID # 4304
(e.g., N000, SLR001, SE1001, etc.)

1. (YES) NO **User Fee Cover Sheet Validated?** **MIS_Elements Screen Change(s):**

2. (YES) NO **APPLICATION CONTAINS CLINICAL DATA?**
(Circle YES if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).

REF **IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION.**

3. YES (NO) **SMALL BUSINESS EXEMPTION**

4. YES (NO) **WAIVER GRANTED**

5. (YES) NO **NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other then bundling).**
If YES, list all NDA #s, review division(s) and those for which an application fee applies.

NDA #	Division		
N 17-970	HFD-150	Fee	No Fee
N 21-109	HFD-510	Fee	(No Fee)

AP'd 30-DEC-1977

6. (YES) NO **BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required**
(Circle YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Circle NO if application should be split into more than one application or be submitted as an original instead of a supplement. If NO, list resulting NDA #s and review division(s).

NDA #	Division	NDA #	Division
N_____	HFD-_____	N_____	HFD-_____

7. (P) S **PRIORITY or STANDARD APPLICATION?**

/S/ 3/4/00
PM Signature / Date

/S/
CPMS Concurrence Signature / Date

2/14/00

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

/s/

Enid Galliers
3/21/02 08:20:55 PM