CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-344

Administrative Documents

EXCLUSIVITY SUMMARY for NDA # 21-344 SUPPL #

Trade Name FASLODEX (fulvestrant) Injection Generic Name

Applicant Name AstraZeneca Pharmaceuticals
HFD- 150
Approval Date 4-26-02

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 / NO /___/

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

      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?

YES /_X_/ NO /___/

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

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

YES /___/ 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 /___/ NO /_X_/

If yes, NDA # _____ Drug Name

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 /_X_/

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 /_X_/

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 /_X_/

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 /___/ 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 /___/ 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 /___/

(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 /___/

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 #

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 /___/

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 /___/

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 #__, Study #

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 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 # _____ YES /___/ NO /___/ Explain:

Investigation #2

IND # _____ 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 /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ 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: _____

_____

_____

/S/

_____

Signature of Preparer Date

Title:

/S/

Signature of Office or Division Director Date

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/

Amy Baird
4/25/02 01:20:20 PM

Richard Pazdur
4/25/02 05:34:54 PM

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 21-344 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-150 Trade and generic names/dosage form: Faslodex (fulvestrant) Injection Action: AP AE NA

Applicant AstraZeneca Pharmaceuticals Therapeutic Class 1P

Indication(s) previously approved N/A
Pediatric information in labeling of approved indication(s) is adequate X inadequate ___

Proposed indication in this application: Faslodex is indicated for the treatment of hormone receptor postive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.
IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)
WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

___ 1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
___ (1) Studies are ongoing,
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes X No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from the medical review
(e.g., medical review, medical officer, team leader).

/S/

Signature of Preparer and Title

Date

cc: Orig NDA/BLA # 21-344
HFD-150/Div File
NDA/BLA Action Package
HFD-960/ Peds Team
(revised 1-14-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 4-7337

Office of Drug Safety

Memo

To: Richard Pazdur, M.D.
Director, Division of Oncology Drug Products
HFD-150

From: Nora Roselle, Pharm.D.
Safety Evaluator, Office of Drug Safety
HFD-400

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
HFD-400

Jerry Phillips, R.Ph.
Associate Director, Office of Drug Safety
HFD-400

CC: Amy Baird
Project Manager, Division of Oncology Drug Products
HFD-150

Date: March 4, 2002

Re: ODS Consult 01-0229-2; Faslodex (Fulvestrant Injection); NDA 21-344

This memorandum is in response to a February 27, 2002, request from your Division to prepare a Phase IV Commitment for the proposed proprietary name, Faslodex. The proposed proprietary name, Faslodex, was found unacceptable by ODS in the initial name review on January 14, 2002 (Consult 01-0229). In addition, DMETS provided a response to a January 22, 2002 request from the sponsor, AstraZeneca, to reconsider the acceptability of the proprietary name Faslodex or accept an alternative name of Faslodex[redacted] DMETS did not recommend the use of either proprietary name in the January 29, 2002 memorandum (Consult 01-0229-1).

In an internal meeting on February 27, 2002 between DMETS and your Division, an agreement was made to consider the proposed proprietary name, Faslodex, acceptable with the following Phase IV commitment incorporated into the final approval package.

Phase IV Commitment:

The sponsor will submit all error reports, both potential and actual, that occur with the drug Faslodex for a period of two years following the date of drug approval. Potential errors include any reports of potential circumstances or events that have the capacity to cause error and should be reported in a quarterly summary. Actual errors include any preventable event that reached the patient and caused harm or reached the patient and did not cause harm. Additionally, the sponsor will report actual errors that occurred but did not reach the patient, such as if the wrong drug was prepared but system checks prevented the drug from reaching the patient or being administered to the patient. All actual errors should be submitted as a 15-day report regardless of patient outcome. The sponsor will agree to provide yearly reports of potential and actual errors occurring with the drug, Faslodex, to the Agency for two years following the date of drug approval.

If you have any questions or need clarification, please contact the medication errors project manager, Sammie Beam at 301-827-3242.

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

/s/

Nora L. Roselle
3/4/02 11:09:48 AM
CSO

Carol Holquist
3/4/02 11:14:50 AM
PHARMACIST

Jerry Phillips
3/5/02 08:15:20 AM
DIRECTOR

Office of Drug Safety

MEMO

To: Richard Pazdur, M.D.
Director, Division of Oncology Drug Products
HFD-150

From: Carol Holquist
Deputy Director, Division of Medication Errors and Technical Support, HFD-400

Through: Jerry Phillips, RPh
Associate Director, Office of Drug Safety, HFD-400

CC: Amy Baird, Project Manager
Division of Oncology Drug Products, HFD-150

Date: January 29, 2002

Re: ODS Consult 01-0229-1; Faslodex (Fulvestrant Injection), NDA #: 21-344

This memorandum is in response to a January 22, 2002, request from the sponsor, AstraZeneca, to reconsider the acceptability of the proprietary name Faslodex or accept an alternative name of Faslodex ~~-~~ The sponsor believes that medication errors will not result from the use of the trade name Faslodex because of the following significant differences between Faslodex and the product trade names Zoladex and Casodex.

Differences in dosage form and dosing schedule:

♦ *Sponsor Comment #1*

There is a significant difference in the dosage form of CASODEX and FOSAMAX compared to FASLODEX. Both CASODEX and FOSAMAX are administered orally as one tablet daily and one tablet daily or weekly, respectively, whereas FASLODEX is dosed intramuscularly on a monthly basis.

DMETS Response

Generally, one would assume that based on these differences in dosage form of these two products the potential for medication errors would be low. However, post-marketing experience has demonstrated that *having differing dosage forms does not eliminate* the potential for error. The Agency has received a number of medication error reports that describe administration of the wrong drug despite that fact that one drug was a tablet and the other an injection. We have also received reported cases of oral solutions administered intravenously. Therefore, based on

previous post-marketing experience, DMETS does not believe that differences in dosage forms or routes of administration necessarily eliminate any potential for confusion when the names clearly sound or look alike to a currently marketed drug product.

♦ *Sponsor Comment #2*
There is a significant difference between the parenteral dosage forms of FASLODEX and ZOLADEX. FASLODEX is an intramuscular injectable solution administered in the buttock, whereas ZOLADEX is a subcutaneous injectable solid depot administered in the abdomen. The needle gauge size for the two is also different. FASLODEX is administered intramuscularly via a 23-gauge SafetyGlide™ needle and ZOLADEX is administered in a disposable syringe device fitted with a 16-gauge hypodermic needle. A health care professional will not administer via the intramuscular route using the ZOLADEX 16-gauge hypodermic needle.

DMETS Response:
The sponsor notes the difference in administration sites (abdomen vs. buttock) and needle size would eliminate the chance of these products being misadministered. However, this statement is unfounded as the Agency has one reported error (ISR 3735202-0) where in fact Zoladex was administered in the buttocks rather than the abdomen.

♦ *Sponsor Comment #3*
There are significant dosing schedule differences between FASLODEX and ZOLADEX. FASLODEX is administered 250 mg monthly (either as a single 5 mL injection or two 2.5 mL injections), whereas ZOLADEX is given at 3.6 mg monthly or 10.8 mg every three months.

DMETS Response
We believe the dosing schedule between Zoladex and Faslodex can be quite similar. Both Zoladex and Faslodex can be administered on a "once monthly" dosing schedule. Although Zoladex is available in two strengths, only *one* strength (3.6 mg) is indicated for the "once monthly" dosing regimen. Therefore, a prescription with a SIG of "once monthly as directed" may not include the corresponding strength. Moreover, confounding factors such as overlapping indications of use (antineoplastics used in breast cancer), injectable dosage forms, and single use syringes exponentially increase the potential for confusion between the two products.

<u>Differences in storage requirements</u>:
♦ *Sponsor Comment #4*
The storage location for FASLODEX is different than the other three products that OPDRA has cited as being too similar. FASLODEX must be refrigerated. The other products are stored at room temperature.

DMETS Response
Storage differences are not an essential factor in the assurance of correct product selection. Medication errors due to sound-alike/look-alike name confusion usually occur upon initial receipt of the prescription. Practitioners cognitively misinterpret the drug product then proceed to dispense, transcribe or administer the incorrect drug product as they believe this is what was intended to be ordered. Upon filling the prescription, the practitioner would proceed to the area in which the incorrect drug product is stored rather than the location of the intended drug product.

Differences in dispensing practices:

♦ *Sponsor Comment #5*

AstraZeneca estimates that approximately 80% of FASLODEX will be given in the Oncologist office setting. Approximately 15% of FASLODEX will be given in the hospital setting, and less then 2% will be in the retail pharmacy setting. Since 80% of the FASLODEX patients will not require a prescription and will be administered drug in an office setting by a nurse, the risk of medication errors will be minimal.

DMETS Response

Errors can occur in any practice setting. According to the sponsor, approximately 17% of Faslodex prescriptions will be dispensed from one of the usual practice settings, hospital or retail. Thus, increasing the number of individuals involved in the medication distribution system. Given the number of variables in these types of distribution systems the likelihood of confusion can be high.

♦ *Sponsor Comment #6*

CASODEX and FOSAMAX are dispensed to a patient from a pharmacy. According to [redacted] of CASODEX units are sold to the retail pharmacy. FASLODEX will be and ZOLADEX is administered almost exclusively in a hospital setting (in or out-patient), or in an outpatient clinic setting (oncologist or urologist's office).

DMETS Response

The sponsor has previously acknowledged that Faslodex will be dispensed from both a retail and hospital setting. Given the look-alike and sound-alike similarities of these product names, in addition to the commonalties cited above, this overlap in dispensing environments only increases the potential for the occurrence of a medication error.

♦ *Sponsor Comment#7*

Urologists and their nurses are very familiar with the unique features of ZOLADEX administration set forth above, including dose and administration technique. This process is very different from the intramuscular injection procedure FASLODEX requires. As a result, patients and nurses, as well as physicians, would be very unlikely to confuse the two products.

DMETS Response

As stated in the response to comment number two above, product nuances are often overlooked and can result in improper administration of the product.

Differences in patient profiles:

♦ *Sponsor Comment #8*

Whereas FASLODEX is expected to be indicated for postmenopausal women with advanced breast cancer, ZOLADEX is primarily used in men with prostate cancer (3.6 and 10.8 mg). In the [redacted] of the patients who received ZOLADEX from a physician were men.

DMETS Response

Zoladex is also indicated for treatment of breast cancer in women. Irregardless of the percentage of patient population this may represent, there is a risk of overlap between patient populations increasing the likelihood of confusion. Additionally, the sponsor has not addressed the potential risk associated with inadvertent administration of Faslodex to a man.

♦ *Sponsor Comment #9*
According to [redacted] of CASODEX prescriptions are written for men, with just over [redacted] written for women. Therefore, the likelihood of a FASLODEX female patient receiving CASODEX is minimal.

DMETS Response
See response to comment eight above.

Differences in visual appearance:
♦ *Sponsor Comment #10*
There are significant differences in the visual appearance of FASLODEX versus ZOLADEX. In addition to differences in the size, shape, and color of the cartons, FASLODEX, a solution, is packaged with 1 or 2 pre-filled syringes in a clear plastic tray. ZOLADEX is a solid depot in a syringe, which is packaged in a brightly colored aluminum pouch. Artwork from the packaging for FASLODEX (2 x 2.5 mL and 1 x 5 mL pre-filled syringe) cartons, ZOLADEX (3.6 mg and 3-Month 10.8 mg) cartons and CASODEX carton are provided in Appendix B. Although not included in Appendix B, the FOSAMAX carton is green and yellow.

DMETS Response
Differences such as those outlined above may not always aid in product distinction especially if it is the first time a patient receives or a practitioner administers the product. Post-marketing reports of medication errors often times describe cases in which the products looked different to the practitioner or patient however they continued to administer the product because they thought it was a generic substitute.

Other:
♦ *Sponsor Comment #11*
Prior to January 15, 2002 discussion, FDA officials never suggested that the tradename FASLODEX might be confused with names of the other approved pharmaceutical products. The trade name FASLODEX was first used in correspondence to FDA in December 1996, and first appeared in scientific literature in July 1997 (Howell A. New endocrine agents. British Journal of Cancer 1997; 76 (Suppl): 13, Abs SP27).

DMETS Response
DMETS begins the review of a proprietary name upon official consult from the review Division. Faslodex was not submitted to DMETS for review and comment until November, 21, 2001. Therefore, we cannot comment further on the timeliness of the submission of the proposed name to the Agency.

Additionally, the sponsor has requested consideration of the alternate name, Faslodex [redacted] We do not believe the addition of the modifier [redacted] will adequately address the sound-alike or look-alike concerns associated with Zoladex. Prescriptions for Faslodex [redacted] may be misinterpreted as Zoladex IM. Although the recommended route of administration of Zoladex is SQ, we have evidence that the product has been administered in the buttocks, a site often reserved for IM injections. Furthermore, physicians may not always remember to include the modifier on the prescription.

In summary, the applicant has failed to provide persuasive data or evidence (i.e., independent analysis of the proposed name utilizing a larger sample size) to minimize the Agency's concern with regard to potential medication errors between Faslodex and Zoladex/Casodex. Based on the lack of supportive data such as an independent analysis of the name and post-marketing experience, DMETS does not recommend the use of the proprietary name Faslodex.

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/s/

Carol Holquist
1/29/02 04:18:51 PM
PHARMACIST

Jerry Phillips
1/29/02 05:05:00 PM
DIRECTOR

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)

DATE RECEIVED: 11/21/01	**DUE DATE:** 01/18/01	**ODS CONSULT #:** 01-0229

TO: Richard Pazdur, M.D.
Director, Division of Oncology Drug Products
HFD-150

THROUGH: Amy Baird
Project Manager
HFD-150

PRODUCT NAME: **Faslodex** (fulvestrant) Injection 125 mg/2.5 mL, 250 mg/5 mL **NDA #:** 21-344	**NDA SPONSOR:** AstraZeneca Pharmaceuticals

SAFETY EVALUATOR: Nora Roselle, PharmD

SUMMARY: In response to a consult from the Division of Oncology Drug Products (HFD-150), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Faslodex" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:
DMETS does not recommend the use of the proprietary name, Faslodex. In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

/S/ /S/

Carol Holquist, RPh
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 14, 2002

NDA NUMBER: 21-344

NAME OF DRUG: Faslodex (fulvestrant) Injection
125 mg/2.5 mL, 250 mg/5 mL

NDA HOLDER: AstraZeneca Pharmaceuticals

I. INTRODUCTION:

This consult was written in response to a request from the Division of Oncology Drug Products (HFD-150), for assessment of the tradename "Faslodex", regarding potential name confusion with other proprietary/generic drug names.

PRODUCT INFORMATION

"Faslodex" is the proposed name for fulvestrant, an intramuscular injection indicated in Draft

'Faslodex" is supplied in sterile single patient pre-filled syringes containing 50 mg/mL fulvestrant, either as a single 5 mL or two concurrent 2.5 mL injections to deliver the required monthly dose. "Faslodex" is administered as an intramuscular injection of 250 mg once monthly.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to Faslodex to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.
[4] WWW location http://www.uspto.gov/tmdb/index.html.
[5] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Faslodex. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified two proprietary names that were thought to have the potential for confusion with Faslodex. Further investigation of the study results also identified an additional product, Fosamax, which may also have potential for confusion with Faslodex. These products are listed in Table 1, along with the dosage forms available and usual dosage.

2. DDMAC did not have concerns about the name with regard to promotional claims.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	**Dosage form(s), Generic name**	**Usual adult dose***	**Other****
Faslodex	Fulvestrant injection, 125 mg/2.5 mL, 250 mg/5 mL	250 mg IM once monthly	
Zoladex	Goserelin Acetate implant injection, 3.6 mg and 10.8 mg single dose syringe	Monthly implant: 3.6 mg injected into upper abdomen every 28 days 3-month implant: 10.8 mg injected into upper abdomen every 12 weeks	*SA
Casodex	Bicalutamide, 50 mg tablet	50 mg by mouth once daily	*SA/LA
Fosamax	Alendronate sodium, 5 mg, 10 mg, 35 mg, 40 mg , 70 mg tablet	Osteoporosis: 10 mg once daily or 70 mg once weekly	*SA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three studies were conducted by DMETS and involved 113 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Faslodex with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Inpatient order and outpatient prescriptions were written, each consisting of marketed and unapproved drug products and a prescription for Faslodex (see page 4). These prescriptions were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal

prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

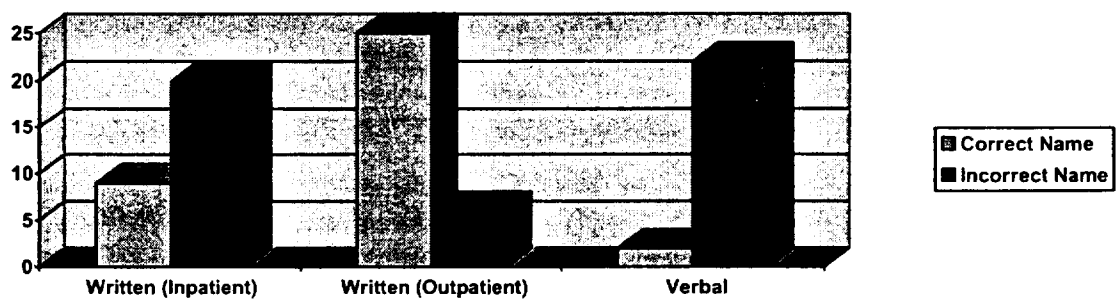
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Faslodex 50 mg/mL 250 mg IM q month #1	Outpatient RX: Faslodex 50 mg/mL Give 250 mg IM once monthly Dispense # 1
Inpatient RX: Faslodex 250 mg IM x 1 today	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written: Inpatient	34	29 (85%)	9 (31%)	20 (69%)
Written: Outpatient	40	31 (78%)	25 (81%)	6 (19%)
Verbal: Outpatient	39	24 (62%)	2 (8%)	22 (92%)
Total	113	84 (74%)	36 (43%)	48 (57%)



Among the written outpatient prescriptions, 6 out of 31 (19%) respondents interpreted "Faslodex" incorrectly. Interpretations included Fasodex, Foslodex, and Fasiodex. One respondent commented that the name "sounds like Casodex". Another respondent also provided the correct name, but commented that the name was "a little like Fosamax".

Among the written inpatient prescriptions, 20 out of 29 (69%) respondents interpreted "Faslodex" incorrectly. The majority of the interpretations were phonetic/misspelled variations of the name, such as Fasodex, Faxlodex, Fascodex, Fosfadex, Faslotex, and Fasgolex.

Among the verbal prescriptions, 22 out of 24 (92%) respondents interpreted "Faslodex" incorrectly. Some of the incorrect interpretations included Fosladex, Fosadex, Fosfadex, Sulfodex, Sufladex, Sulfadex, Phosla-Dex, Phaclodex, and Phosphodex. None of the incorrect interpretations included names of marketed drug products. As in the written outpatient responses, one study participant stated that the name "sort of sounded like Fosamax".

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Faslodex", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. The products considered having the greatest potential for name confusion with Faslodex were Casodex and Zoladex. Further investigation of the study results also identified an additional product, Fosamax, which may also have potential for confusion with Faslodex.

Zoladex is the proprietary name for goserelin acetate, an antineoplastic agent. Zoladex and Faslodex sound similar to one another. Zoladex and Faslodex are both hormonal antineoplastic agents that can be used in the treatment of breast cancer. Zoladex is commonly used in the palliative treatment of prostate cancer, endometriosis, and pre/perimenopausal breast cancer. Faslodex is indicated in the treatment of postmenopausal breast cancer. Both Zoladex and Faslodex are drug products that require a prescription from a physician. Likewise, both drugs are commonly given as once a month injections. Because both Zoladex and Faslodex are commonly dosed as once a month injections, physicians may write "use as directed, dispense one", hence adding to the potential for confusion between these two drugs. Zoladex is prescribed in both men and women, but Faslodex is only used in women. Even though there are differences in strength and patient population between the two drugs, the likelihood of confusion and error is serious if a male patient inadvertently receives Faslodex instead of Zoladex.

Casodex is the proprietary name for bicalutamide, which is an antineoplastic agent indicated in the treatment of advanced prostatic carcinoma. One study respondent commented that the drug name "sounds like Casodex". Each name has three syllables and contains the "dex" ending. Likewise, the similar combinations of beginning letters, "Caso" and "Faslo", sound alike when pronounced aloud. Not only do Casodex and Faslodex sound similar to one another, the drug names look similar when scripted as well.

Both Casodex and Faslodex are antineoplastic agents available under the direct care of a physician. Casodex is available as a **50** mg tablet and is dosed as one tablet once daily. Similarly, Faslodex is also available in the same number strength (**50** mg/mL), and is dosed as 250 mg once monthly intramuscular injection. Confusion may occur if a physician writes a prescription for "Faslodex 250 mg, use as directed", as there is a possibility that a patient may inadvertently receive five times the usual dose of Casodex if the handwriting is not readable. Casodex is indicated for the treatment of prostate cancer and Faslodex is used in the treatment of postmenopausal breast cancer. Thus, even though there are differences that exist between the two drugs, the consequences of a medication error between the two drugs is potentially serious and life threatening.

A review of the drug name study indicated that two respondents stated that the name "sort of sounded like Fosamax" and is "a little like Fosamax". Fosamax is the tradename for alendronate sodium, used in the treatment of osteoporosis in postmenopausal women and Paget's Disease.

Fosamax is dosed either once daily by mouth (5 mg, 10 mg, 40 mg) or once a week by mouth (35 mg, 70 mg). Faslodex is dosed once a month intramuscularly. Fosamax is available as an oral tablet and Faslodex is available as an intramuscular injection. Both drugs are used in women, but have different indications for use. Confusion between the two seems unlikely given the differences in dosage form, dosage strength, and indication for use.

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proposed proprietary name Faslodex.

In reviewing the proprietary name "Faslodex", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. The products considered having the greatest potential for name confusion with Faslodex were Casodex and Zoladex.

Zoladex is the proprietary name for goserelin acetate, an antineoplastic agent. Zoladex and Faslodex sound similar to one another. Zoladex and Faslodex are both hormonal antineoplastic agents that can be used in the treatment of breast cancer. Zoladex is commonly used in the palliative treatment of prostate cancer, endometriosis, and pre/perimenopausal breast cancer. Faslodex is indicated in the treatment of postmenopausal breast cancer. Both Zoladex and Faslodex are drug products that require a prescription from a physician. Likewise, both drugs are commonly given as once a month injections. Because both Zoladex and Faslodex are commonly dosed as once a month injections, physicians may write "use as directed, dispense one", hence adding to the potential for confusion between these two drugs. Zoladex is prescribed in both men and women, but Faslodex is only used in women. Even though there are differences in strength and patient population between the two drugs, the likelihood of confusion and error is serious if a male patient inadvertently receives Faslodex instead of Zoladex.

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Both Casodex and Faslodex are antineoplastic agents available under the direct care of a physician. Casodex is available as a **50** mg tablet and is dosed as one tablet once daily. Similarly, Faslodex is also available in the same number strength (**50** mg/mL), and is dosed as 250 mg once monthly intramuscular injection. Confusion may occur if a physician writes a prescription for "Faslodex 250 mg, use as directed", as there is a possibility that a patient may inadvertently receive five times the usual dose of Casodex if the handwriting is not readable. Casodex is indicated for the treatment of prostate cancer and Faslodex is used in the treatment of postmenopausal breast cancer. Thus, even though there are differences that exist between the two drugs, the consequences of a medication error between the two drugs is potentially serious and life threatening.

In the review of the syringe labels, carton and insert labeling of Faslodex, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has reviewed the current syringe labels, carton and insert labeling and has identified several areas of possible improvement, which might minimize potential user error.

A. SYRINGE LABEL (2.5 mL, 5 mL)

1. 2.5 mL

   a. We recommend that the strength be expressed as "125 mg/2.5 mL" with the "50 mg/mL" located directly beneath or immediately following the total strength.

   b. Increase the prominence of the statement " Both syringes must be administered to receive the 250 mg recommended monthly dose."

2. 5 mL

   a. We recommend that the strength be expressed as "250 mg/5 mL" with the "50 mg/mL" located directly beneath or immediately following the total strength.

B. CARTON LABELING (2.5 mL, 5 mL)

1. 2.5 mL

   a. See comment 1a under SYRINGE LABEL.

   b. We recommend that the total content statement, on the principal display and back panels, be revised to read "Each carton contains TWO pre-filled syringes. Each syringe contains 125 mg/2.5 mL (50 mg/mL) fulvestrant." In addition, we recommend the inclusion of the statement " Both syringes must be administered to receive the 250 mg recommended daily dose."

   c. We recommend that the side panels be revised to read "Two pre-filled syringes each containing 125 mg/2.5 mL".

   d. We recommend that Step 2 of the "INSTRUCTIONS FOR USE" be revised to read "Peel open the SafetyGlide™ outer packaging. For complete SafetyGlide™ instruction refer to prescribing information."

   e. We recommend that Step 7 of the "INSTRUCTIONS FOR USE" be revised to read "Administer intramuscularly slowly in the buttock."

   f. We recommend the addition of Step 10 to the "INSTRUCTIONS FOR USE" section to read "Both syringes must be administered to receive the 250 mg recommended daily dose."

   g. We recommend relocating the statement "PLEASE NOTE: The syringes are supplied half full. Both syringes must be administered to receive the 250 mg recommended monthly dose" to appear in conjunction with the "USUAL DOSAGE" statement.

2. 5 mL

a. See comment 2a under SYRINGE LABEL.

b. We recommend the revision of the back label to read "Carton contains: One 5 mL pre-filled syringe containing 5 mL or 250 mg (50 mg/mL) of fulvestrant..."

c. As per 21 CFR 201.100(b)(5), revise the "Faslodex also contains..." statement to include the quantitative measurements of the inactive ingredients.

d. See comment 1d under CARTON LABELING.

e. See comment 1e under CARTON LABELING.

C. INSERT LABELING

1. DOSAGE AND ADMINISTRATION SECTION

a. We recommend in Step 2 of the "Instructions for use and handling and disposal" inclusion of the following sentence "For complete SafetyGlide™ instruction refer below to the "Directions for Use of SafetyGlide™.""

b. We recommend revising Step 7 of the "Instructions for use and handling and disposal" to read " Administer intramuscularly slowly in the buttock."

2. DIRECTIONS FOR USE OF SAFETYGLIDE™

a. We note that you refer to figures 3,4, and 5 throughout this section of the labeling. However, the draft insert provided for review contains only three figures. We recommend renumbering to begin with the number one.

b. We recommend the addition of another step to say the following "When dispensing the 125 mg/2.5 mL syringe, both syringes must be administered to receive the 250 mg recommended monthly dose."

IV. RECOMMENDATIONS:

DMETS does not recommend the use of the proprietary name Faslodex.

DMETS recommends the above labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3231.

/S/

Nora Roselle, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

DF

MEMORANDUM of MEETING

DATE: January 24, 1997 **TIME:** 1:30-3 pm Location: Conf "G" WOC2

IND/DRUG [redacted] Faslodex (ZD9238)

SPONSOR: Zeneca

MEETING PURPOSE: End-of-Phase 2 Meeting
Indication: [redacted]

draft

PARTICIPANTS:

FDA
Robert Justice, M.D., Deputy Director
Julie Beitz, M.D., Acting Team Leader
Karen Johnson, M.D., Medical Officer
David McGuinn, Ph.D. Pharmacologist
W. Schmidt, Ph.D., Pharmacology, Acting Team Leader
T. Koutsoukos, Ph.D., Statistics
Gene Williams, Ph.D., Pharmacokinetics
Atiqur Rahman, Ph.D., Pharmacokinetics, Team Leader
Rebecca Wood, Ph.D., Chemist, Team Leader
Josephine Jee, Chemist,
James Krook, M.D., ODAC consultant by phone
Leslie Vaccari, Project Manager

Zeneca
Robert Milsted, M.D., International Group Manager
Steven Averbuch, M.D., Project Physician
Mohammed Azab, M.D., International Project Physician
Jill Davis, International Project Biometrician
Mike Harrison, Drug Kinetics Project Manager
Frances Kelleher, Ph.D., Manager, Drug Regulatory Affairs
[redacted]
Robert Siddall, International Project Toxicologist
Alan Wakeling, Ph.D., Research Associate
David Taylor, Ph.D., Product Development Group, Section Manager
Derek Young, Ph.D., Analytic Chemist
Angela Milne, Regulatory Project Team Leader

DISCUSSION POINTS with DECISIONS (Agreements) REACHED

1. Based on the information presented, the development of this diasteroisomer mixture is justified and acceptable.

2. The formulation (using castor oil, benzyl benzoate, benzyl alcohol and ethanol) is acceptable from a chemistry standpoint. From a pharmacology standpoint, additional information, including the rationale and risk patients incur for the maximum dose of benzyl benzoate/benzoic moiety (0.5 mg/kg/day over the 1 month duration between injections), must be provided in the application.

3. Dr. McGuinn stated that the data suggests that ICI 182,780 may be an antiestrogen with little agonist activity but conclusive determination is not possible at this time. This will be determined during the review of the NDA.

Dr. McGuinn added that except for the reprotoxicity data, the pharmacology/toxicology evaluation appears complete. For this indication, segment II reproduction toxicity studies in two species will be needed. For the adjuvant claim, full reproductive toxicology and DNA adduct data will be necessary.

4. Further FDA review of the formulation release data remains to be completed. Dr. Williams will convey comments and recommendations as soon as available. Zeneca confirmed that there is no plan or expectation that the formulation will be changed in any way.

5. It is acceptable to study an i.v. formulation in volunteers and patients in order to characterize the full pharmacokinetic profile, especially the elimination phase. Full single and multiple dose pk data using the LA i.m. formulation will be recorded in breast cancer patients.

6. The design and necessity of the special population studies will depend on the outcome of a mass balance study and metabolic profile evaluation which must be completed.

   a. A liver impairment study using an i.v. formulation is acceptable.

   b. If it can be demonstrated that renal excretion of drug and metabolites is insignificant, a renal impairment study will not be conducted.

   c. Specific studies in elderly patients will not be conducted because the pivotal efficacy studies are expected to recruit post-menopausal patients across a range of ages. We recommend that sampling include more than 60 patients and include both trough sampling and sampling on Day 21.

7. Drugs to be studied for drug interaction will be selected from *in vitro* work. Drug interaction work in healthy male volunteers will be done using an i.v. formulation. Safety studies in patients will be undertaken as work in volunteers suggests clinical significance. Information should also be provided which is collected from adverse event monitoring. Ideally sampling of patients with serious events should be done.

8. The use of a [redacted] method for analysis of pharmacokinetic samples is acceptable, subject to demonstration that the administered diasteroisomer ratio does not change.

9. The proposed program including Study/Protocol 9238IL/0020 and Study/Protocol 9238IL/0021 is acceptable. (Refer to attached one-page summary of each protocol.)

   The choice of Arimidex as the comparator was discussed and is acceptable but the FDA and Dr. Krook continued to prefer that one study include Megace as a comparator.

   In addition to a double-blind, placebo-controlled trial in the United States, a second open label study in Europe is adequate as a pivotal trial, but the FDA would prefer to see two blinded studies.

Time to progression is an acceptable primary endpoint only if superiority is being demonstrated. Time to Response (TTR) should also be evaluated.

Some of the statistical issues were noted. In addition, Dr. Koutsoukos stated he will provide a complete and detailed review of the statistical plan by February 7. (Review was conveyed to Zeneca by facsimile February 4, 1997.)

ACTION ITEMS:

1. Zeneca will submit the overheads used during meeting.

2. Ms. Vaccari will convey the statistical review of the statistical plan as soon as possible and no later that Feb 7: will convey the comments and recommendations by Dr. Williams on the formulation release data: and minutes of the meeting when finalized.

The meeting was concluded at 2:55 pm. There were no unresolved discussion points.

/S/ 2-7-97 Concurrence /S/ 3/7/97
Project Manager
Minutes preparer

Attachment: Overheads

cc.
Original IND —
HFD-150/Div File
HFD-150/KJohnson
HFD-150/WDMcGuinn
HFD-150/GeWilliams
HFD-150JJee
HFD-150/TKoutsoukos
HFD-150/LVaccari
HFD-150/DPease

Drafted by: LVaccari/1-31-97
R/D init. by: KJohnson/3-3-97
GeWilliams/2-12-97
WDMcGuinn/2-10-97
JBeitz/3-4-97
JJee/2-3-97
RWood/2-4-97
TKoutsoukos/2-12-97
WSchmidt/2-11-97

Study/Protocol: 9238IL/0021: A Double-blind, Randomized, Phase II/III Multicenter Trial Comparing the Efficacy and Tolerability of 125 mg and 250 mg of Long-Acting ICI 182,780 (Faslodex) With 1 mg of Anastrozole (Arimidex) in Postmenopausal Women With Advanced Breast Cancer

Purpose of study: To compare the effect of two dosages of Faslodex with one dosage of Arimidex in Postmenopausal women with advanced breast cancer in terms of time to Progression and other secondary endpoints

Design: Double-blind, multicenter, multinational, randomized, parallel group

Population: Postmenopausal women with advanced breast cancer who have relapsed or progressed after adjuvant endocrine therapy or following first-line endocrine therapy for advanced disease

Schema: Arm 1: 125 mg (1 x 2.5 ml) Faslodex im monthly + placebo tablet po od
Arm II: 250 mg (2 x 2.5 ml) Faslodex im monthly + placebo tablet po od
Arm III: 1 mg Arimidex po od + placebo (I x 2.5 ml or 2 x 2.5 ml) im monthly

Endpoints:
Primary: Time to progression (TTP)
Secondary: Objective tumor response (OTR), duration of response (DOR), time to treatment failure (TTF), time to death (TTD), to tolerability (T), quality of life (QOL), symptomatic response (SR), Pharmacokinetics (PK)

Definitions: TTP: time from randomization to documented progression; OTR: proportion of subjects with a best response of complete response or partial response; DOR: time from randomization to documented progression in subjects having an OTR; TTF: time from randomization to either progression or withdrawal for any reason including death from any cause; TTD: time from randomization to death; T : summary of adverse events; QOL: total outcomes index of FACT-B instrument; SR: summary of analgesic use, global pain score, and performance status; PK: standard pharmacokinetic profile based on blood concentrations

Statistical Plan:
Sample size: n = 196 per treatment group (n = 588 total)
Analyses: Intent to treat all randomized patients, secondary analysis of patients as treated less violators identified by sponsor; 5% significance level applies to both comparisons
Tests on primary and secondary endpoints: TTP, TTD, TTF - Cox's proportional hazards regression model adjusting for covariates,OTR- logistic regression model adjusting for covariates, QOL - Analysis of Covariance
Interim analysis: 1) After 30 patients accrued on low dose arm and followed for 3 months. Purpose - to determine clinical activity of this arm. 2) After 100 patients accrued to each arm and followed for 6 month. Purpose - to confirm clinical activity of Faslodex and ensure its safety

Estimated start and completion dates: Enrollment from March 1997 to September 1999.

Study/Protocol 9238IL/0020: An Open, Randomized, Phase II/III Multicenter Trial Comparing the Efficacy and Tolerability of 125 mg and 250 mg of Long-Acting ICI 182,780 (Faslodex) With mg of Anastrozole (Arimidex) in Postmenopausal Women With Advanced Breast Cancer

Purpose of study: To compare the effect of two dosages of Faslodex with one dosage of Arimidex in postmenopausal women with advanced breast cancer in terms of time to progression

Design: Open, multicenter, randomized, parallel group

Population: Postmenopausal women with advanced breast cancer who have relapsed or progressed after adjuvant endocrine therapy or following first-line endocrine therapy for advanced disease

Schema: Arm 1: 125 mg (1 x 2.5 ml) Faslodex im monthly
Arm II: 250 mg (1 x 5 ml) Faslodex im monthly
Arm III: 1 mg Arimidex po od

Endpoints:

Primary: Time to progression (TTP)

Secondary: Objective tumor response (OTR), duration of response (DOR), time to treatment failure (TTF), time to death (TTD), tolerability (T), quality of life (QOL), symptomatic response (SR), Pharmacokinetics (PK)

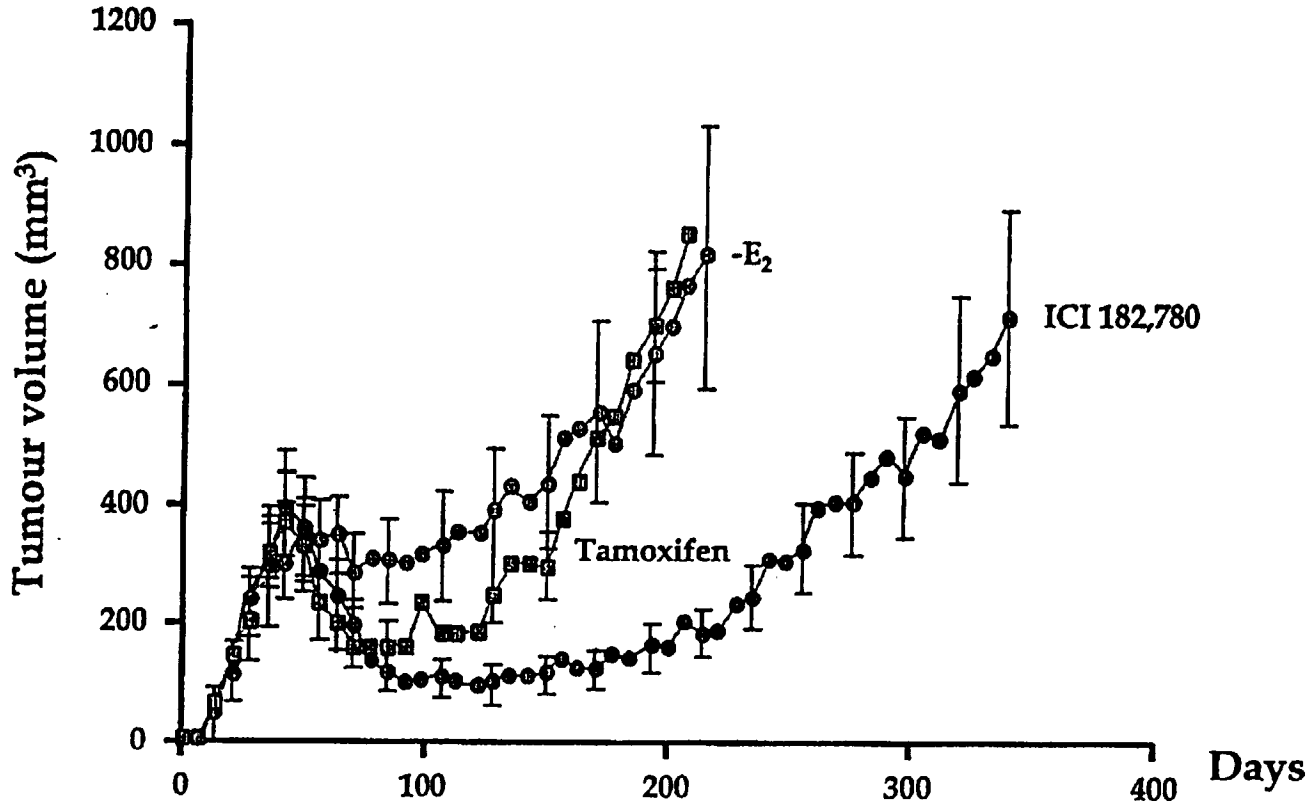
Definitions: TTP: time from randomization to documented progression; OTR: proportion of subjects with a best response of complete response or partial response; DOR: time from randomization to documented progression in subjects having an OTR; TTF: time from randomization to either progression or withdrawal for any reason including death from any cause; TTD: time from randomization to death; T : summary of adverse events; QOL: total outcomes index of FACT-B instrument; SR: summary of analgesic use, global pain score, and performance status; PK: standard pharmacokinetic profile based on blood concentrations

Statistical Plan:

Sample size: n = 196 per treatment group (n = 588 total)
Analyses: intent to treat all randomized patients, secondary analysis of patients as treated less violators identified by sponsor; 5% significance level applies to both comparisons
Tests on primary and secondary endpoints: TTP, TTD, TTF - Cox's proportional hazards regression model adjusting for covariates, OTR logistic regression model adjusting for covariates, QOL - Analysis of Covariance
Interim analysis: 1) After 30 patients accrued on low dose arm and followed for 3 months. purpose - to determine clinical activity of this arm. 2) After 100 patients accrued to each arm and followed for 6 month. Purpose - to confirm clinical activity of Faslodex and ensure its safety.

Estimated start and completion dates: enrollment from March 1997 to September 1999.

Effects of estrogen withdrawal, tamoxifen, and ICI 182,780 on MCF-7 tumour growth

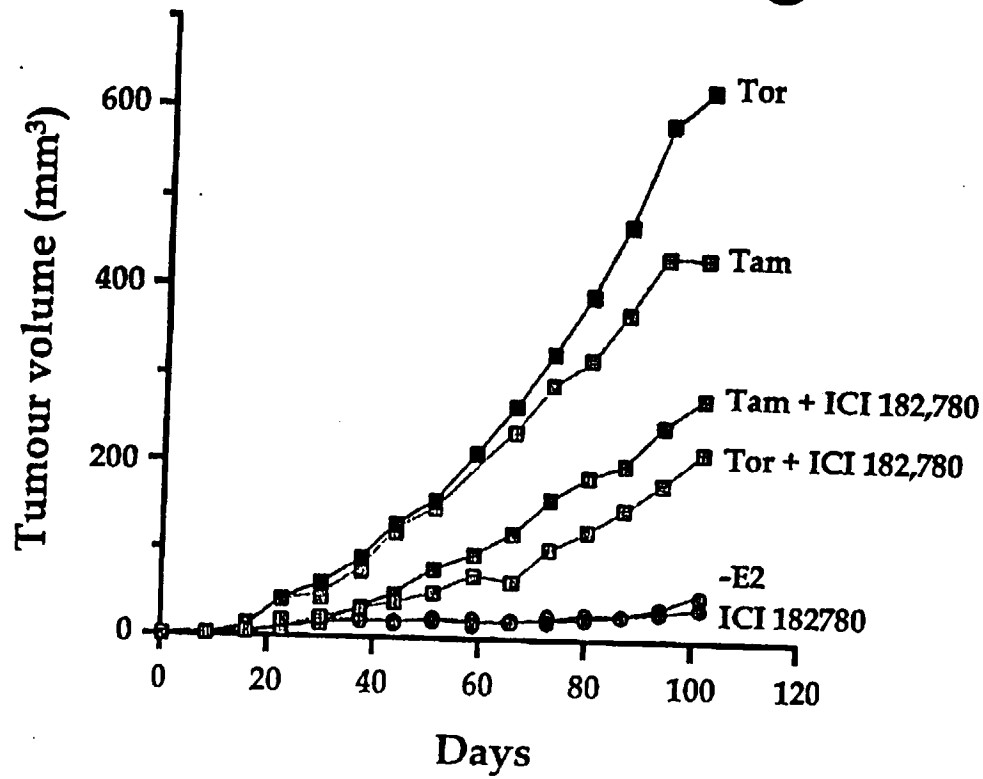


- Estrogen-supplemented mice were inoculated with MCF-7 cells. On day 36 when tumours had formed, mice were randomly allocated to treatment by withdrawal of estrogen (-E_2; -● -); withdrawal of estrogen and treatment with 500 µg tamoxifen given once a day, Monday through Friday (- ■ -); or 5 mg ICI 182,780 given once a week (-● -). Tumour volumes were determined at the times show. n=10 mice per group; means ± SE.

  [Osborne et al., J. Nat. Cancer Inst. (1995), 87, 746]

(2)

Effect of ICI 182,780 on tamoxifen-stimulated tumour growth



- Mice (10/group) received either ICI 182,780 at 5 mg/mouse per week s.c. alone or combined with tamoxifen or toremifene

  [Osborne et al., Cancer Chemother Pharmacol (1994) 34, 89]

Proposed Indication

Draft

Pre-INDUSTRY MEETING MINUTES

MEETING DATE: October 9, 2001 **TIME:** 3:00pm **LOCATION:** B

IND/NDA NDA 21-344

Meeting Request Submission Date: 8-31-01
Briefing Document Submission Date: 9-28-01
Additional Submission Dates: 10-12-01

DRUG: FASLODEX (fulvestrant) Injection

SPONSOR/APPLICANT: AstraZeneca Pharmaceuticals

TYPE OF MEETING:

1. NDA Review Status.

2. **Proposed Indication:** Draft

FDA PARTICIPANTS:

Richard Pazdur, M.D., Director, HFD-150
Grant Williams, M.D., Clinical Team Leader, HFD-150
Peter Bross, M.D., Clinical Reviewer, HFD-150
Josephine Jee, Chemistry Reviewer, DNDC1
David Morse, Ph.D., Supervisory Pharmacologist, HFD-150
Lilliam Rosario, Ph.D., Pharmacology Reviewer, HFD-150
Gang Chen, Ph.D., Statistical Team Leader, HFD-150
Peiling Yang, Ph.D., Statistical Reviewer, HFD-150
Gene Williams, Ph.D., Biopharmaceutical Reviewer, HFD-150
Amy Baird, Consumer Safety Officer, HFD-150

MEETING OBJECTIVES:

1. Discuss sponsor's questions in briefing documents dated 9-28-01 and 8-31-01.

QUESTIONS for DISCUSSION with FDA RESPONSE:

1. **Does FDA agree that the approvability of NDA 21-344 does not depend on the results from Trial 0025?**

FDA Response:

- Registration for the second line indication is generally not affected by results of trials in other indications unless significant safety issues are identified. Please provide the safety data for trial 025.

2. **In the last two weeks, AstraZeneca was informed that due to the world situation, scheduled selected Division of Scientific Investigations activities have been postponed. AstraZeneca notes that part of the September 11, 2001 Oncology Drug Advisory Committee meeting was canceled. AstraZeneca is concerned about the impact of world events on the FASLODEX Prescription Drug User Fee Act (PDUFA) date. Can FDA comment on any impact at this time?**

FDA Response:

- At this time the FDA does not plan to modify the existing PDUFA date for Faslodex.

3. **Has FDA identified any deficiencies during their review of the NDA thus far (e.g., non-inferiority)?**

FDA Response:

- Safety review is ongoing, but thus far no significant deficiencies have been identified. There were minor discrepancies found in response categorization of a few patients, which have not affected the overall conclusions. With a non-inferiority margin of 10% the FDA preliminary analysis agrees with the sponsor that fulvestrant 250 mg was non-inferior to anastrozole with respect to best objective response rate in trials #20 and #21. With a non-inferiority margin of 25%, the FDA preliminary analysis agrees with the sponsor that fulvestrant 250-mg was non-inferior to anastrozole with respect to time to progression in trials #20 and #21.

4. **What are the potential questions regarding fulvestrant to be presented for discussion before the Oncology Drugs Advisory Committee?**

FDA Response:

- We are considering taking action on this NDA without presenting the application to the ODAC.

5. **With regard to the problems associated with a statistical comparison of Duration of Response (DoR) between treatment groups which is based on responding patients only (see correspondence from FDA dated March 9, 1999), AstraZeneca has, subsequent to NDA filing, developed an approach to the analysis of DoR which is based on the method proposed by Begg and Larson (1982).**

   Begg and Larson indicate that a "probability of being in response (PBR) curve" may be constructed for each treatment group. This curve is based on the data for all randomized patients, thereby avoiding the problem of a subgroup of patients (responders) which is treatment-outcome dependent. The area under the PBR curve for each treatment group may be calculated, and AstraZeneca proposes that treatment groups may be compared by calculating the ratio of the AUCs, together with the corresponding confidence interval.

   Would FDA be prepared to consider the results of such an analysis for inclusion in the review of the Faslodex NDA and possible labeling?

FDA Response:

- Such analysis would be considered exploratory and is unlikely to be included in labeling.

Follow-Up:

FDA responses were faxed to the sponsor 10-9-01. AstraZeneca sought clarification of a couple of our responses in a facsimile of 10-12-01 (see attached). Per the FDA facsimile of 10-15-01 (see attached) which provided responses to the 10-12-01 sponsor fax, AstraZeneca requested to cancel the scheduled industry meeting of 10-16-01.

The pre-meeting was concluded at 4:30pm.

/S/

Amy Baird
Project Manager
Minutes Preparer

Concurrence Chair: /S/

Grant Williams, M.D.
Clinical Team Leader

Attachments: Sponsor's facsimile dated 10-12-01.
FDA facsimile of 10-15-01.

INTERNAL MEETING MINUTES

MEETING DATE: November 9, 2000 **TIME:** 9:30am **LOCATION:** B

IND/NDA IND [redacted]

Meeting Request Submission Date: 9-14-00
Briefing Document Submission Date: 10-20-00
Additional Submission Dates:

DRUG: Faslodex

SPONSOR/APPLICANT: AstraZeneca Pharmaceuticals

TYPE OF MEETING:

1. Pre-NDA.

2. **Proposed Indication:** Treatment · Draft [redacted]

FDA PARTICIPANTS:

Richard Pazdur, M.D., Director, HFD-150
Grant Williams, M.D., Clinical Team Leader, HFD-150
Peter Bross, M.D., Clinical Reviewer, HFD-150
Susan Honig, M.D., Clinical Reviewer, HFD-150
Gang Chen, Ph.D., Statistical Team Leader, HFD-150
Amy Baird, Project Manager, HFD-150

MEETING OBJECTIVES:

1. Discuss sponsor's questions in briefing document dated 10-20-00.

APPEARS THIS WAY
ON ORIGINAL

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Two Phase III trials compared fulvestrant with anastrozole in postmenopausal women with advanced breast cancer whose disease had relapsed or progressed following adjuvant endocrine therapy for first-line endocrine therapy for advanced disease.

The objectives and designs of these 2 pivotal trials are described in Table 1 and are similar. Because the trials had the same end points and used the same statistical methods, the results were similar and reproducible.

The median time to progression for patients treated with fulvestrant was 5.5 months in both trials. Tumor response was 20.7% and 18.0% in Trials 0020 and 0021, respectively. The median times to progression for anastrozole were 5.1 and 3.5 months in Trials 0020 and 0021, respectively, and the proportions of patients with tumor response were 15.7% and 17.5%, respectively.

In Trial 21, the double-blind trial conducted in North America, preliminary results (See Section 3) for the primary end point, time to disease progression, show an estimated hazard ratio (fulvestrant/anastrozole) of 0.91 (2-sided 95.14% confidence interval = 0.73-1.13; upper 1-sided 95% confidence limit = 1.09). In Trial 0020, the open trial conducted outside North America, the estimated hazard ratio was 0.98 (2-sided 95.14% confidence interval = 0.80-1.21; upper 1-sided 95% confidence limit = 1.16).

Previous US regulatory submissions for hormonal treatments for advanced breast cancer (FARESTON [toremifene], October 1995; ARIMIDEX [anastrozole], September 2000) required that the upper 1-sided confidence limit for the hazard ratio for time to progression not exceed 1.25 in order to demonstrate noninferiority; ie, a potential deficiency of more than 25% for the experimental treatment should be ruled out. The upper 1-sided 95% confidence limits allow a greater than 16% in Trial 0020 to be ruled out. AstraZeneca believes that both trials allow a clinically important deficiency for fulvestrant to be ruled out in terms of time to disease progression.

In terms of tumor response (Table 3), the 2 regulatory submissions cited above required a deficiency in response rate of greater than 10% to be ruled out in order to demonstrate noninferiority. The lower 1-sided 95% confidence limit for the difference in response rates in Trial 0021 allows a potential deficiency for fulvestrant of greater than 5.3% to be ruled out. For Trial 0020, the lower 1-sided 95% confidence limit indicates that a potential deficiency for fulvestrant of greater than 1.2% may be ruled out.

Given the observed response rate of 17.5% for anastrozole in Trial 0021, the lower confidence limit indicates that at least 70% of this response rate is preserved by fulvestrant. In Trial 0020, the lower confidence limit indicates that at least 92% of the observed response rate of 15.7% for anastrozole is preserved by fulvestrant.

1. **Using the above approach, does the FDA agree that noninferiority for time to progression and tumor response has been demonstrated for both Trials 0021 and 0020?**

FDA Response:

- Prior regulatory experience with this class of drugs has focused on response rate as the primary endpoint for approval.
- Focus on non-inferiority of response rate.
- TTP considered as a secondary endpoint for review.
- One-sided 97.5% CI should be used in non-inferiority analyses.

The overall similarity of the safety profile based on combined data from the 2 pivotal trials and the reproducibility of the efficacy data for both time to progression and tumor response suggest that the balance of risks and benefits is at least as good for fulvestrant as it is for anastrozole.

2. **Based on the analysis performed to date, AstraZeneca believes that both the safety and efficacy data from the pivotal trials described in this briefing document is sufficient to support filing an original NDA for FASLODEX for the indication, '** [redacted] **Does the FDA agree?**

FDA Response:

- The safety and efficacy data appear sufficient to support filing. Questions regarding content and format of electronic submissions can be addressed to esub@cder.fda.gov.
- Wording of indication is a review issue.

3. **Fulvestrant is a new class of anticancer agent which reduces levels of estrogen-receptor protein in human tumor cells by a process known as downregulation. The mode of action of this steroidal antiestrogen is distinct from that of selective estrogen-receptor modulators (SERMs) with mixed agonist and antagonist properties. Fulvestrant lacks the partial agonism of tamoxifen, is not expected to cause endometrial stimulation, and is effective in tamoxifen-resistant disease. In the pivotal Phase III trials, clinical efficacy of fulvestrant is at least as good as that of anastrozole. AstraZeneca believes fulvestrant will provide meaningful therapeutic benefit to postmenopausal women with breast cancer. The new class of drug and distinction from SERMs and good safety profile of fulvestrant suggest a priority review. Does the FDA agree?**

FDA Response:

- Priority review status designation requires that a drug be a significant improvement over existing therapeutic options. This decision will be made within 60 days after receipt of the submission of the NDA.

S

Amy Baird
Project Manager
Minutes Preparer

Concurrence Chair: S

Peter Bross, M.D.
Clinical Reviewer

cc:
Orig. IND —
HFD-150/Div. File

TELEPHONE CONFERENCE MEETING MINUTES

MEETING DATE: August 3, 2000 **TIME:** 3:30pm **LOCATION:** B

IND/NDA [redacted]

Meeting Request Submission Date: 6-5-00
Briefing Document Submission Date: 6-5-00
Additional Submission Dates:

DRUG: Faslodex

SPONSOR/APPLICANT: AstraZeneca

TYPE OF MEETING:

1. Pre-NDA

2. **Proposed Indication:** DRAFT [redacted]

FDA PARTICIPANTS:

Richard Pazdur, M.D., Director, HFD-150 (pre-only)
Grant Williams, M.D., Clinical Team Leader, HFD-150
Peter Bross, M.D., Clinical Reviewer, HFD-150
Dave McGuinn, Ph.D., Pharmacology Reviewer, HFD-150
Ning Li, Ph.D., Statistical Reviewer, HFD-150
Atiqur Rahman, Ph.D., Biopharm Team Leader, HFD-150
Gene Williams, Ph.D., Biopharm Reviewer, HFD-150
Amy Baird, Project Manager, HFD-150

INDUSTRY PARTICIPANTS:

Kathy Gans-Brangs, Ph.D.
E. Jane Valas, Ph.D.
Alan Webster, MSc.
Richard Hellmund, MSc.
Dr. Moris
Dr. White
Dr. Harrison

MEETING OBJECTIVES:

1. Discuss sponsor's questions in meeting package dated 6-5-00.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. Does the FDA agree that AstraZeneca has demonstrated comparability of 1 injection and 2 injections based on the PK parameters, and that the submission is acceptable for filing?

FDA Response:

- This issue will not prevent the application from being filed. You have not established bioequivalence between the 2 injection schedules. Please address this issue in your study report.

- Please clarify how many patients in each trial received each injection schedule. You may want to discuss with the Division additional analyses based on this breakdown.

- 1 x 5 mL injection is not bioequivalent to 2 x 2.5 mL injections.

AstraZeneca response per submission dated 8-2-00 (serial # 105):

"In Trial 20, all patients randomized to fulvestrant received a single 5 mL injection (250 mg) in one buttock monthly."

In Trial 21, all patients randomized to fulvestrant received a 2.5 mL injection (125 mg) in each buttock at the same time monthly.

Therefore, the only difference in the method of administration of 250 mg fulvestrant between the two trials is that 250 mg fulvestrant was administered as a single 5 mL injection in one trial and two 2.5 mL concurrently administered injections in the other.

The original intent of the pharmacokinetic component of Trials 20 and 21, as described in our End of Phase II Briefing Document (Serial # 001), was that drug exposure obtained using two methods of administration of 250 mg of fulvestrant would be assessed by non-randomized evaluation of pharmacokinetic data. Subsequently, it became clear that AstraZeneca obtained less pharmacokinetic data than anticipated. We then undertook Trial 39 (draft Clinical Trial Report Summary attached as Tab A), which was a randomized, comparative trial, and concluded that we have a more robust evaluation of pharmacokinetics parameters than originally proposed.

As noted previously in the Pre-NDA briefing document (Serial # 072), it was not our intention to demonstrate formal bioequivalence between 1 x 5 mL and 2 x 2.5 mL dosing techniques. While we agree with the Division that formal bioequivalence has not been shown in Trial 39, the evidence from Trial 39 does not suggest any difference in terms of exposure between these dosing techniques. Formal bioequivalence considerations do not

appear to be applicable to the use of fulvestrant because the parenteral dosage from for Trials 20 and 21 contained the same dose and used the same pharmaceutical form.

Trials 20 and 21 were prospectively designed to allow a combined efficacy analysis of the pivotal trials. We believe the data from Trial 39 supports this combined efficacy analysis.

Does FDA agree with this approach to the combined efficacy analysis of Trials 20 and 21 or is further clarification required at the teleconference scheduled for Thursday, 3 August 2000 at 3:30pm?

FDA Response:

- Combined efficacy analysis is not acceptable, as these studies are "stand alone" trials. Therefore, efficacy analysis of Trials 20 and 21 should be 2 separate analyses. A combined analysis would be considered exploratory.

- Combined analysis of safety data is acceptable.

2. **The indication sought for FASLODEX in the original NDA is,** [redacted] **The NDA will be submitted without a specific hepatic impairment study because of the reasons described above. Appropriate labeling will be sought for patients similar to those treated in Trials 0020 and 0021, including those with mild-moderate hepatic impairment related to liver metastases. Does the FDA agree that the NDA is acceptable for filing without a specific hepatic impairment study?**

FDA Response:

- Yes.

3. **Does FDA agree that PDF format is acceptable for Case Report Form Tabulations as indicated above?**

FDA Response:

- Yes. All of the information that is recorded on the case report forms for the main trials (0004, 0020, 0021, and 0039) should be included in the electronic data as SAS transport files. If not, please specify in advance of the NDA submission which you proposed to omit from the datasets. We assume that annotated case

report forms (example CRFs mapping each CRF entry to the location of the data in the datasets) will be provided to allow reviewers to decipher the data.

Additional Comments:

The Division is piloting a new process for orienting the review team to new NDAs. We invite you to give a 1-hour presentation of your NDA to the Division of Oncology Drug Products about 2 weeks after the NDA is submitted. This may be followed by 30 minutes of questions and discussion. This is to provide the entire review team with an early summary of your perspective and to allow clarification of potential problems or misperceptions.

The Division may wish to schedule appointments with you to answer questions from individual reviewers regarding format or location of information in either the paper or electronic portions of the NDA.

The telephone conference ended at 4:45pm. There were no unresolved issues or discussion points.

/S/

Amy Baird
Project Manager
Minutes Preparer

Concurrence Chair: /S/

Peter Bross, M.D.
Clinical Reviewer

cc:
Orig. IND [redacted]
HFD-150/Div. File

/s/

Peter Bross
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