CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021344Orig1s012

Trade Name:	FASLODEX
Generic or Proper Name:	fulvestrant solution for injection
Sponsor:	AstraZeneca Pharmaceuticals LP
Approval Date:	September 9, 2010
Change:	For changing the dosage of FASLODEX from 250 mg to 500 mg.

CENTER FOR DRUG EVALUATION AND RESEARCH

021344Orig1s012

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s012

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021344/S-007/S-012

SUPPLEMENT APPROVAL

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

Dear Mr. Troise:

Please refer to your Supplemental New Drug Applications (sNDA) dated December 1, 2005 and November 12, 2009, received December 2, 2005 and November 13, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Faslodex® (fulvestrant) Solution for Injection.

We acknowledge receipt of your amendments dated January 24, 2006, September 28, 2006, April 25, 2007, March 4, 2010, March 24, 2010 and May 14, 2010. This supplement provides for revisions regarding Hepatic Impairment to the following sections of the label: Dosage and Administration, Warnings & Precautions, Special Populations and Clinical Pharmacology. These revisions are based on results from trial 9238IL/0063.

We have completed our review of supplement 007, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We also acknowledge receipt of your amendments dated November 16, 2009, December 22, 2009, December 23, 2009, January 21, 2010, February 1, 2010, March 15, 2010, April 19, 2010, May 10, 2010, May 12, 2010, May 21, 2010, June 25, 2010, July 7, 2010, August 6, 2010, August 12, 2010, August 13, 2010, August 25, 2010, August 26, 2010, September 1, 2010, September 7, 2010 and September 8, 2010. This sNDA provides for changing the dosage of Faslodex® from 250 mg to 500 mg.

We have completed our review of supplement 012, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is

identical to the enclosed labeling (text for the package insert, text for the patient package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted on September 1, 2010, as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 021344/012**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Alberta Davis-Warren, Regulatory Project Manager, at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, M.D.
Deputy Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ
NDA-21344	SUPPL-7	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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

/s/

AMNA IBRAHIM
09/09/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s012

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FASLODEX® safely and effectively. See full prescribing information for FASLODEX.

FASLODEX® *(fulvestrant) injection*

INITIAL US APPROVAL: 2002

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Recommended Dose (2.1), 09/2010
Dosage and Administration, Dose Modification (2.2), 09/2010
Dosage and Administration, Administration Technique (2.3), 09/2010

----------INDICATIONS AND USAGE----------

FASLODEX is an estrogen receptor antagonist indicated for the:

- Treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

----------DOSAGE AND ADMINISTRATION----------

- FASLODEX 500 mg should be administered intramuscularly into the buttocks slowly (1 - 2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29 and once monthly thereafter. (2.1, 14)
- A dose of 250 mg is recommended in patients with moderate hepatic impairment to be administered intramuscularly into the buttock slowly (1- 2 minutes) as one 5 mL injection on days 1, 15, 29 and once monthly thereafter. (2.2, 5.2, 8.6)

----------DOSAGE FORMS AND STRENGTHS----------

FASLODEX, an injection for intramuscular administration, is supplied as 50 mg/mL fulvestrant. (3)

----------CONTRAINDICATIONS----------

- Hypersensitivity (4)

----------WARNINGS AND PRECAUTIONS----------

- Blood Disorders: Should be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use. (5.1)
- Hepatic Impairment: A 250 mg dose is recommended in patients with moderate hepatic impairment (2.2, 5.2, 8.6)
- Pregnancy: Fetal harm can occur when administered to a pregnant woman. Women should be advised of the potential hazard to the fetus and to avoid becoming pregnant while receiving FASLODEX. (5.3)

----------ADVERSE REACTIONS----------

- The most common, clinically significant adverse reactions occurring in ≥ 5% of patients receiving FASLODEX 500 mg were: injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flash, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea, and constipation. (6.1)
- Increased hepatic enzymes (ALT, AST, ALP) occurred in >15% of FASLODEX patients and were not dose-dependent.

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www fda.gov/medwatch for voluntary reporting of adverse reactions

----------DRUG INTERACTIONS----------

- There are no known drug-drug interactions**.** (7)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing Mothers: discontinue drug or nursing taking into account the importance of drug to the mother. (8.3)

SEE 17 FOR PATIENT COUNSELING INFORMATION AND FDA-APPROVED PATIENT LABELING

Revised: 09/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FASLODEX is indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose is 500 mg to be administered intramuscularly into the buttocks slowly (1 - 2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29 and once monthly thereafter *[see Clinical Studies (14)]*.

2.2 Dose Modification

Hepatic Impairment:
A dose of 250 mg is recommended for patients with moderate hepatic impairment (Child-Pugh class B) to be administered intramuscularly into the buttock slowly (1 - 2 minutes) as one 5 mL injection on days 1, 15, 29 and once monthly thereafter.

FASLODEX has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C) *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*.

2.3 Administration Technique

The proper method of administration of FASLODEX for intramuscular use is described in the instructions that follow:

1. Remove glass syringe barrel from tray and check that it is not damaged.
2. Remove perforated patient record label from syringe.
3. Peel open the safety needle (SafetyGlide™) outer packaging. For complete SafetyGlide™ instructions refer below to the "Directions for Use of SafetyGlide™".
4. Break the seal of the white plastic cover on the syringe luer connector to remove the cover with the attached rubber tip cap (see Figure 1).
5. Twist to lock the needle to the luer connector.
6. Remove needle sheath.
7. Remove excess gas from the syringe (a small gas bubble may remain).
8. Administer intramuscularly slowly in the buttock.
9. Immediately activate needle protection device upon withdrawal from patient by pushing lever arm completely forward until needle tip is fully covered (see Figure 2).

10. Visually confirm that the lever arm has fully advanced and the needle tip is covered. If unable to activate, discard immediately into an approved sharps collector.
11. Repeat steps 1 through 10 for second syringe.

How To Use FASLODEX.

For the 2 x 5 mL syringe package, the contents of both syringes must be injected to receive the 500 mg recommended dose.

SAFETYGLIDE™ INSTRUCTIONS FROM BECTON DICKINSON

SafetyGlide™ is a trademark of Becton Dickinson and Company

Reorder number 305917

CAUTION CONCERNING SAFETYGLIDE™

Federal (USA) law restricts this device to sale by or on the order of a physician. To help avoid HIV (AIDS), HBV (Hepatitis), and other infectious diseases due to accidental needlesticks, contaminated needles should not be recapped or removed, unless there is no alternative or that such action is required by a specific medical procedure.

WARNING CONCERNING SAFETYGLIDE™

Do not autoclave SafetyGlide™ Needle before use. Hands must remain behind the needle at all times during use and disposal.

DIRECTIONS FOR USE OF SAFETYGLIDE™

For each syringe:

Remove glass syringe barrel from tray and check that it is not damaged.

Peel apart packaging of the SafetyGlide™, break the seal of the white plastic cover on the syringe Luer connector and attach the SafetyGlide™ needle to the Luer Lock of the syringe by twisting.

Transport filled syringe to point of administration.

Pull shield straight off needle to avoid damaging needle point.

Administer injection following package instruction.

For user convenience, the needle 'bevel up' position is orientated to the lever arm, as shown in Figure 3.

Immediately activate needle protection device upon withdrawal from patient by pushing lever arm completely forward until needle tip is fully covered (Figure 2).

Visually confirm that the lever arm has fully advanced and the needle tip is covered. If unable to activate, discard immediately into an approved sharps collector.

Activation of the protective mechanism may cause minimal splatter of fluid that may remain on the needle after injection.

For greatest safety, use a one-handed technique and activate away from self and others.

After single use, discard in an approved sharps collector in accordance with applicable regulations and institutional policy.

Becton Dickinson guarantees the contents of their unopened or undamaged packages to be sterile, non-toxic and non-pyrogenic.

Figure 1

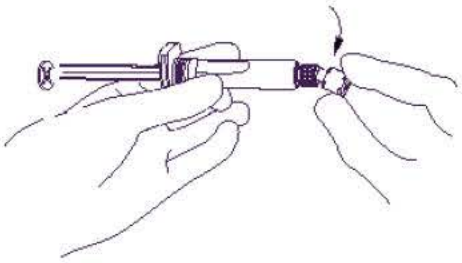


Figure 2

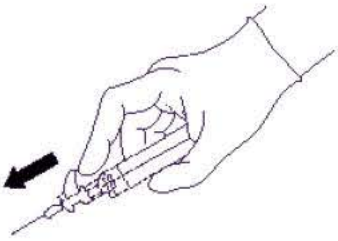
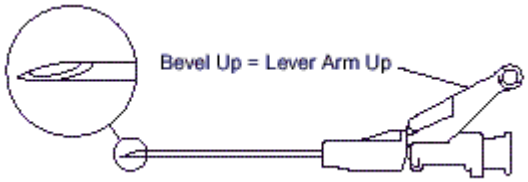


Figure 3



3 DOSAGE FORMS AND STRENGTHS

FASLODEX, an injection for intramuscular administration, is supplied as 5-mL prefilled syringes containing 50 mg/mL fulvestrant.

4 CONTRAINDICATIONS

FASLODEX is contraindicated in patients with a known hypersensitivity to the drug or to any of its components. Hypersensitivity reactions, including urticaria and angioedema, have been reported in association with FASLODEX.

5 WARNINGS AND PRECAUTIONS

5.1 Blood Disorders

Because FASLODEX is administered intramuscularly, it should be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use.

5.2 Hepatic Impairment

The safety and pharmacokinetics of FASLODEX were evaluated in a study in seven subjects with moderate hepatic impairment (Child-Pugh class B) and seven subjects with normal hepatic function. Exposure was increased in patients with moderate hepatic impairment, therefore a dose of 250 mg is recommended *[see Dosage and Administration (2.2)]*.

FASLODEX has not been studied in patients with severe hepatic impairment (Child-Pugh class C) *[see Use in Specific Populations (8.6)]*.

5.3 Use in Pregnancy

Based on its mechanism of action and findings in animals, FASLODEX can cause fetal harm when administered to a pregnant woman. Fulvestrant caused fetal loss or abnormalities in animals when administered during the period of organogenesis at doses significantly smaller than the maximum recommended human dose based on the body surface area. There are no adequate and well-controlled studies in pregnant women using FASLODEX. Women of childbearing potential should be advised not to become pregnant while receiving FASLODEX. If FASLODEX is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

Comparison of FASLODEX 500 mg and FASLODEX 250 mg

The following frequency categories for adverse reactions (ARs) were calculated based on the safety analysis of Study 1 that compared FASLODEX 500 mg with FASLODEX 250 mg. The most frequently reported adverse reactions in the fulvestrant 500 mg group were injection site pain (11.6% of patients), nausea (9.7% of patients) and bone pain (9.4% of patients); the most frequently reported adverse reactions in the fulvestrant 250 mg group were nausea (13.6% of patients), back pain (10.7% of patients) and injection site pain (9.1% of patients).

Table 1 lists adverse reactions reported with an incidence of 5% or greater, regardless of assessed causality, from the controlled clinical trial Study 1 comparing the administration of FASLODEX 500 mg intramuscularly once a month with FASLODEX 250 mg intramuscularly once a month.

Table 1: Summary of Most Commonly Reported Adverse Reactions in Study 1 (≥ 5% in either treatment group): Safety Population

Body System and Adverse Reaction	Number (%) of Patients	
	Fulvestrant 500 mg N=361	**Fulvestrant 250 mg** N=374
Body as a Whole		
Injection Site Pain	42 (11.6)	34 (9.1)
Headache	28 (7.8)	25 (6.7)
Back Pain	27 (7.5)	40 (10.7)
Fatigue	27 (7.5)	24 (6.4)
Pain in Extremity	25 (6.9)	26 (7.0)
Asthenia	21 (5.8)	23 (6.1)
Vascular System		
Hot Flash	24 (6.6)	22 (5.9)
Digestive System		
Nausea	35 (9.7)	51 (13.6)
Vomiting	22 (6.1)	21 (5.6)
Anorexia	22 (6.1)	14 (3.7)
Constipation	18 (5.0)	13 (3.5)
Musculoskeletal System		
Bone Pain	34 (9.4)	28 (7.5)
Arthralgia	29 (8.0)	29 (7.8)
Musculoskeletal Pain	20 (5.5)	12 (3.2)
Respiratory System		
Cough	19 (5.3)	20 (5.3)
Dyspnea	16 (4.4)	19 (5.1)

In the pooled safety population (N=1127) from clinical trials comparing FASLODEX 500 mg to FASLODEX 250 mg, post-baseline increases of ≥1 CTC grade in either AST, ALT, or alkaline phosphatase were observed in > 15% of patients receiving FASLODEX. Grade 3-4 increases were observed in 1-2% of patients. The incidence and severity of increased hepatic enzymes (ALT, AST, ALP) did not differ between the 250 mg and the 500 mg FASLODEX arms.

Comparison of FASLODEX 250 mg and Anastrozole 1 mg in Combined Trials (Studies 2 and 3)

The most commonly reported adverse reactions in the FASLODEX and anastrozole treatment groups, regardless of the investigator's assessment of causality, were gastrointestinal symptoms (including nausea, vomiting, constipation, diarrhea and abdominal pain), headache, back pain, vasodilatation (hot flashes), and pharyngitis.

Injection site reactions with mild transient pain and inflammation were seen with FASLODEX and occurred in 7% of patients (1% of treatments) given the single 5 mL injection (predominantly European Trial Study 3) and in 27% of patients (4.6% of treatments) given the 2 x 2.5 mL injections (North American Trial Study 2).

Table 2 lists adverse reactions reported with an incidence of 5% or greater, regardless of assessed causality, from the two controlled clinical trials comparing the administration of FASLODEX 250 mg intramuscularly once a month with anastrozole 1 mg orally once a day.

Table 2: Combined Data from Studies 2 and 3, Adverse Reactions ≥ 5%

Body System and Adverse Reaction[a]	**FASLODEX 250 mg N=423 (%)**	**Anastrozole 1 mg N=423 (%)**
Body as a Whole	68.3	67.6
Asthenia	22.7	27.0
Pain	18.9	20.3
Headache	15.4	16.8
Back Pain	14.4	13.2
Abdominal Pain	11.8	11.6
Injection Site Pain[b]	10.9	6.6
Pelvic Pain	9.9	9.0
Chest Pain	7.1	5.0
Flu Syndrome	7.1	6.4
Fever	6.4	6.4
Accidental Injury	4.5	5.7
Cardiovascular System	30.3	27.9
Vasodilatation	17.7	17.3
Digestive System	51.5	48.0
Nausea	26.0	25.3
Vomiting	13.0	11.8
Constipation	12.5	10.6
Diarrhea	12.3	12.8
Anorexia	9.0	10.9
Hemic and Lymphatic Systems	13.7	13.5
Anemia	4.5	5.0
Metabolic and Nutritional Disorders	18.2	17.7
Peripheral Edema	9.0	10.2
Musculoskeletal System	25.5	27.9
Bone Pain	15.8	13.7

Arthritis	2.8	6.1
Nervous System	34.3	33.8
Dizziness	6.9	6.6
Insomnia	6.9	8.5
Paresthesia	6.4	7.6
Depression	5.7	6.9
Anxiety	5.0	3.8
Respiratory System	38.5	33.6
Pharyngitis	16.1	11.6
Dyspnea	14.9	12.3
Cough Increased	10.4	10.4
Skin and Appendages	22.2	23.4
Rash	7.3	8.0
Sweating	5.0	5.2
Urogenital System	18.2	14.9
Urinary Tract Infection	6.1	3.5

[a]A patient may have more than one adverse reaction.
[b]All patients on FASLODEX received injections, but only those anastrozole patients who were in the North American Study 2 received placebo injections.

6.2 Post-Marketing Experience

For FASLODEX 250 mg, other adverse reactions reported as drug-related and seen infrequently (<1%) include thromboembolic phenomena, myalgia, vertigo, leukopenia, and hypersensitivity reactions including angioedema and urticaria.

Vaginal bleeding has been reported infrequently (<1%), mainly in patients during the first 6 weeks after changing from existing hormonal therapy to treatment with FASLODEX. If bleeding persists, further evaluation should be considered.

7 DRUG INTERACTIONS

There are no known drug-drug interactions. Although, fulvestrant is metabolized by CYP 3A4 *in vitro*, drug interactions studies with ketoconazole or rifampin did not alter fulvestrant pharmacokinetics. Dose adjustment is not needed in patients co-prescribed CYP3A4 inhibitors or inducers *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see 'Warnings and Precautions' section]*

FASLODEX can cause fetal harm when administered to a pregnant woman. Fulvestrant caused fetal loss or abnormalities in animals when administered during the period of organogenesis at doses significantly smaller than the maximum recommended human dose based on the body surface area (BSA). Women of childbearing potential should

be advised not to become pregnant while receiving FASLODEX. If FASLODEX is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

In studies in female rats at intramuscular doses ≥ 0.01 mg/kg/day (0.6% of the human recommended dose based on BSA), fulvestrant caused a reversible reduction in female fertility, as well as effects on embryo-fetal development consistent with its antiestrogenic activity. Fulvestrant caused an increased incidence of fetal abnormalities in rats (tarsal flexure of the hind paw at 2 mg/kg/day; equivalent to the human dose based on BSA) and non-ossification of the odontoid and ventral tubercle of the first cervical vertebra at doses ≥ 0.1 mg/kg/day (6% the human dose based on BSA) when administered during the period of organogenesis. Rabbits failed to maintain pregnancy when dosed intramuscularly with 1 mg/kg/day fulvestrant (equivalent to the human dose based on BSA) during the period of organogenesis. Further, in rabbits dosed at 0.25 mg/kg/day (30% the human dose based on BSA), increases in placental weight and post-implantation loss were observed. Fulvestrant was associated with an increased incidence of fetal variations in rabbits (backwards displacement of the pelvic girdle, and 27 pre-sacral vertebrae at 0.25 mg/kg/day; 30% the human dose based on BSA) when administered during the period of organogenesis. Because pregnancy could not be maintained in the rabbit following doses of fulvestrant of 1 mg/kg/day and above, this study was inadequate to fully define the possible adverse effects on fetal development at clinically relevant exposures.

8.3 Nursing Mothers

It is not known if fulvestrant is excreted in human milk. Fulvestrant is found in rat milk at levels significantly higher (approximately 12-fold) than plasma after administration of 2 mg/kg. Drug exposure in rodent pups from fulvestrant-treated lactating dams was estimated as 10% of the administered dose. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from FASLODEX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

For FASLODEX 250 mg, when tumor response was considered by age, objective responses were seen in 22% and 24% of patients under 65 years of age and in 11% and 16% of patients 65 years of age and older, who were treated with FASLODEX in Study 2 and Study 3, respectively.

8.6 Hepatic Impairment

FASLODEX is metabolized primarily in the liver.

The pharmacokinetics of fulvestrant were evaluated after a single dose of 100 mg in subjects with mild and moderate hepatic impairment and normal hepatic function (n = 7 subjects/group), using a shorter-acting intramuscular injection formulation. Subjects with mild hepatic impairment (Child-Pugh class A) had comparable mean AUC and clearance values to those with normal hepatic function. In subjects with moderate hepatic impairment (Child-Pugh class B) the average AUC of fulvestrant increased by 70% compared to patients with normal hepatic function. AUC was positively correlated with total bilirubin concentration (p = 0.012). FASLODEX has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

A dose of FASLODEX 250 mg is recommended in patients with moderate hepatic impairment (Child-Pugh class B) *[see Dosage and Administration (2.2) and Warning and Precautions (5.2)]*.

8.7 Renal Impairment

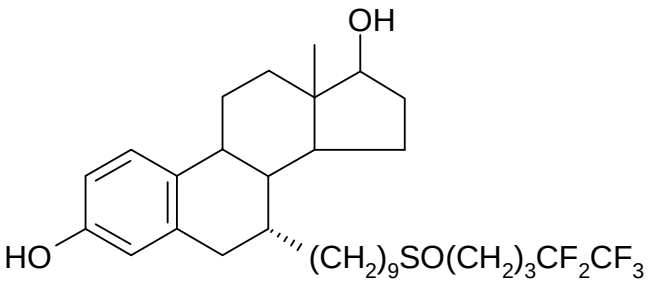
Negligible amounts of fulvestrant are eliminated in urine; therefore, a study in patients with renal impairment was not conducted. In the advanced breast cancer trials, fulvestrant concentrations in women with estimated creatinine clearance as low as 30 mL/min were similar to women with normal creatinine.

10 OVERDOSAGE

Animal studies have shown no effects other than those related directly or indirectly to antiestrogen activity with intramuscular doses of fulvestrant higher than the recommended human dose. There is no clinical experience with overdosage in humans. No adverse reactions were seen in healthy male and female volunteers who received intravenous fulvestrant, which resulted in peak plasma concentrations at the end of the infusion, that were approximately 10 to 15 times those seen after intramuscular injection.

11 DESCRIPTION

FASLODEX® (fulvestrant) Injection for intramuscular administration is an estrogen receptor antagonist. The chemical name is 7-alpha-[9-(4,4,5,5,5-penta fluoropentylsulphinyl) nonyl]estra-1,3,5-(10)- triene-3,17-beta-diol. The molecular formula is $C_{32}H_{47}F_5O_3S$ and its structural formula is:



Fulvestrant is a white powder with a molecular weight of 606.77. The solution for injection is a clear, colorless to yellow, viscous liquid.

Each injection contains as inactive ingredients: 10% w/v Alcohol, USP, 10% w/v Benzyl Alcohol, NF, and 15% w/v Benzyl Benzoate, USP, as co-solvents, and made up to 100% w/v with Castor Oil, USP as a co-solvent and release rate modifier

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Many breast cancers have estrogen receptors (ER) and the growth of these tumors can be stimulated by estrogen. Fulvestrant is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner with affinity comparable to that of estradiol and downregulates the ER protein in human breast cancer cells.

In vitro studies demonstrated that fulvestrant is a reversible inhibitor of the growth of tamoxifen-resistant, as well as estrogen-sensitive human breast cancer (MCF-7) cell lines. In *in vivo* tumor studies, fulvestrant delayed the establishment of tumors from xenografts of human breast cancer MCF-7 cells in nude mice. Fulvestrant inhibited the growth of established MCF-7 xenografts and of tamoxifen-resistant breast tumor xenografts.

Fulvestrant showed no agonist-type effects in *in vivo* uterotropic assays in immature or ovariectomized mice and

rats. In *in vivo* studies in immature rats and ovariectomized monkeys, fulvestrant blocked the uterotrophic action of estradiol. In postmenopausal women, the absence of changes in plasma concentrations of FSH and LH in response to fulvestrant treatment (250 mg monthly) suggests no peripheral steroidal effects.

12.2 Pharmacodynamics

In a clinical study in postmenopausal women with primary breast cancer treated with single doses of FASLODEX 15-22 days prior to surgery, there was evidence of increasing down-regulation of ER with increasing dose. This was associated with a dose-related decrease in the expression of the progesterone receptor, an estrogen-regulated protein. These effects on the ER pathway were also associated with a decrease in Ki67 labeling index, a marker of cell proliferation.

12.3 Pharmacokinetics

Absorption

The single dose and multiple dose PK parameters for the 500 mg dosing regimen with an additional dose (AD) at Day 15 are reported in Table 3. The additional dose of FASLODEX given two weeks after the initial dose allows for steady state concentrations to be reached within the first month of dosing.

Table 3: Summary of fulvestrant pharmacokinetic parameters [gMean (CV%)] in postmenopausal advanced breast cancer patients after intramuscular administration 500 mg + AD dosing regimen

		C_{max} (ng/mL)	**C_{min} (ng/mL)**	**AUC (ng hr/mL)**
500 mg + AD*	Single dose	25.1(35.3)	16.3(25.9)	11400 (33.4)
	Multiple dose steady state**	28.0(27.9)	12.2(21.7)	13100(23.4)

* additional 500 mg dose given on day 15

** month 3

Distribution:

The apparent volume of distribution at steady state is approximately 3 to 5 L/kg. This suggests that distribution is largely extravascular. Fulvestrant is highly (99%) bound to plasma proteins; VLDL, LDL and HDL lipoprotein fractions appear to be the major binding components. The role of sex hormone-binding globulin, if any, could not be determined.

Metabolism:

Biotransformation and disposition of fulvestrant in humans have been determined following intramuscular and intravenous administration of ^{14}C-labeled fulvestrant. Metabolism of fulvestrant appears to involve combinations of a number of possible biotransformation pathways analogous to those of endogenous steroids, including oxidation, aromatic hydroxylation, conjugation with glucuronic acid and/or sulphate at the 2, 3 and 17 positions of the steroid nucleus, and oxidation of the side chain sulphoxide. Identified metabolites are either less active or exhibit similar activity to fulvestrant in antiestrogen models.

Studies using human liver preparations and recombinant human enzymes indicate that cytochrome P-450 3A4 (CYP 3A4) is the only P-450 isoenzyme involved in the oxidation of fulvestrant; however, the relative contribution of P-450 and non-P-450 routes *in vivo* is unknown.

Excretion:

Fulvestrant was rapidly cleared by the hepatobiliary route with excretion primarily via the feces (approximately 90%). Renal elimination was negligible (less than 1%). After an intramuscular injection of 250 mg, the clearance (Mean ± SD) was 690 ± 226 mL/min with an apparent half-life about 40 days.

Special Populations:

Geriatric:

In patients with breast cancer, there was no difference in fulvestrant pharmacokinetic profile related to age (range 33 to 89 years).

Gender:

Following administration of a single intravenous dose, there were no pharmacokinetic differences between men and women or between premenopausal and postmenopausal women. Similarly, there were no differences between men and postmenopausal women after intramuscular administration.

Race:

In the advanced breast cancer treatment trials, the potential for pharmacokinetic differences due to race have been evaluated in 294 women including 87.4% Caucasian, 7.8% Black, and 4.4% Hispanic. No differences in fulvestrant plasma pharmacokinetics were observed among these groups. In a separate trial, pharmacokinetic data from postmenopausal ethnic Japanese women were similar to those obtained in non-Japanese patients.

Pediatric:
The pharmacokinetics of fulvestrant have not been evaluated in pediatric patients.

Drug-Drug Interactions:
There are no known drug-drug interactions. Fulvestrant does not significantly inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2C19, 2D6, and 3A4 *in vitro*, and studies of co-administration of fulvestrant with midazolam indicate that therapeutic doses of fulvestrant have no inhibitory effects on CYP 3A4 or alter blood levels of drug metabolized by that enzyme. Although fulvestrant is partly metabolized by CYP 3A4, a clinical study with rifampin, an inducer of CYP 3A4, showed no effect on the pharmacokinetics of fulvestrant. Also results from a healthy volunteer study with ketoconazole, a potent inhibitor of CYP3A4, indicated that ketoconazole had no effect on the pharmacokinetics of fulvestrant and dosage adjustment is not necessary in patients co-prescribed CYP 3A4 inhibitors or inducers *[see Drug Interactions (7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year carcinogenesis study was conducted in female and male rats, at intramuscular doses of 15 mg/kg/30 days, 10 mg/rat/30 days and 10 mg/rat/15 days.

These doses correspond to 0.9-, 1.5-, and 3-fold (in females) and 0.8-, 0.8-, and 2-fold (in males) the systemic exposure [$AUC_{0\text{-}30\ days}$] achieved in women receiving the recommended dose of 500 mg/month. An increased incidence of benign ovarian granulosa cell tumors and testicular Leydig cell tumors was evident, in females dosed at 10 mg/rat/15 days and males dosed at 15 mg/rat/30 days, respectively. Induction of such tumors is consistent with the pharmacology-related endocrine feedback alterations in gonadotropin levels caused by an antiestrogen.

Fulvestrant was not mutagenic or clastogenic in multiple *in vitro* tests with and without the addition of a mammalian liver metabolic activation factor (bacterial mutation assay in strains of Salmonella typhimurium and Escherichia coli, *in vitro* cytogenetics study in human lymphocytes, mammalian cell mutation assay in mouse lymphoma cells and *in vivo* micronucleus test in rat).

In female rats, fulvestrant administered at doses ≥ 0.01 mg/kg/day (0.6% the human recommended dose based on body surface area [BSA]), for 2 weeks prior to and for 1 week following mating, caused a reduction in fertility and embryonic survival. No adverse effects on female fertility and embryonic survival were evident in female animals dosed at 0.001 mg/kg/day (0.06% the human dose based on BSA). Restoration of female fertility to values similar to controls was evident following a 29-day withdrawal period after dosing at 2 mg/kg/day (equivalent to the human dose based on BSA). The effects of fulvestrant on the fertility of female rats appear to be consistent with its antiestrogenic activity. The potential effects of fulvestrant on the fertility of male animals were not studied but, in a 6-month toxicology study, male rats treated with intramuscular doses of 15 mg/kg/30 days, 10 mg/rat/30 days, or 10 mg/rat/15 days fulvestrant showed a loss of spermatozoa from the seminiferous tubules, seminiferous tubular atrophy, and degenerative changes in the epididymides. Changes in the testes and epididymides had not recovered 20 weeks after cessation of dosing. These fulvestrant doses correspond to 1.3-, 1.2- and 3.5-fold the systemic exposure [$AUC_{0\text{-}30\ days}$] achieved in women receiving the recommended dose of 500 mg/month.

14 CLINICAL STUDIES

The efficacy of FASLODEX 500 mg versus FASLODEX 250 mg was compared in Study 1. The efficacy of FASLODEX 250 mg was compared to anastrozole in Studies 2 and 3.

Comparison of FASLODEX 500 mg and FASLODEX 250 mg (Study 1)

A Phase 3 randomized, double-blind, controlled clinical trial (Study 1) was completed in 736 postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. This trial compared the efficacy and safety of FASLODEX 500 mg (n=362) with FASLODEX 250 mg (n=374).

FASLODEX 500 mg was administered as two 5 mL injections each containing FASLODEX 250 mg/5mL, one in each buttock, on Days 1, 15, 29 and every 28 (+/- 3) days thereafter. FASLODEX 250 mg was administered as two 5 mL injections (one containing FASLODEX 250 mg/5mL injection plus one placebo injection), one in each buttock, on Days 1, 15 (2 placebo injections only), 29 and every 28 (+/-3) days thereafter.

The median age of study participants was 61. All patients had ER+ advanced breast cancer. Approximately 30% of subjects had no measurable disease. Approximately 64% of patients had visceral disease.

Results of Study 1 after a minimum follow-up duration of 18 months are summarized in Table 4. The efficacy of FASLODEX 500 mg was compared to that of FASLODEX 250 mg. Figure 1 shows a Kaplan-Meier plot of the Progression Free Survival (PFS) data demonstrating statistically significant superiority of FASLODEX 500 mg vs FASLODEX 250 mg. Figure 2 shows a Kaplan-Meier plot of the Overall Survival (OS) data. There was no statistically significant difference in OS between the two treatment groups.

Table 4: Efficacy Results Study 1: Intent To Treat (ITT) Population

Endpoint	**Fulvestrant 500 mg (N=362)**	**Fulvestrant 250 mg (N=374)**
PFS[a] Median (months)	6.5	5.4
Hazard Ratio[b] (95% CI[c])	0.80 (0.68-0.94)	
p-value	0.006	
OS[d] Died	175 (48.3)	203 (54.3)
Median OS (months)	25.1	22.8
Hazard Ratio[b] (95% CI[c])	0.84 (0.69-1.03)	
ORR[e] (95% CI[c])	13.8% (9.7%, 18.8%) (33/240)	14.6% (10.5%, 19.4%) (38/261)

[a] PFS (Progression Free Survival) = the time between randomization and the earliest of progression or death from any cause.

[b] Hazard ratio < 1 favors FASLODEX 500 mg.

[c] CI = Confidence Interval

[d] OS = Overall Survival

[e] ORR (Objective Response Rate), defined as number (%) of patients with complete response or partial response, was analyzed in the evaluable patients with measurable disease at baseline (fulvestrant 500 mg N=240; fulvestrant 250 mg N=261).

Figure 1: Kaplan-Meier PFS: Study 1 ITT Population

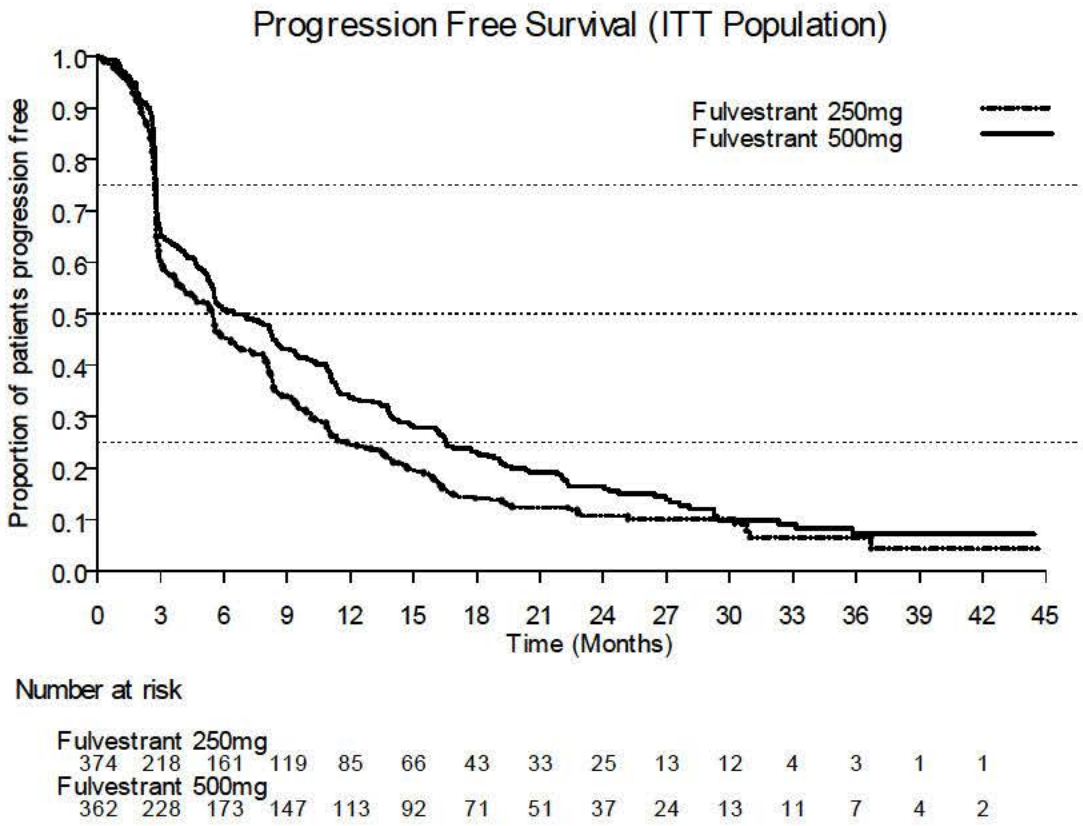
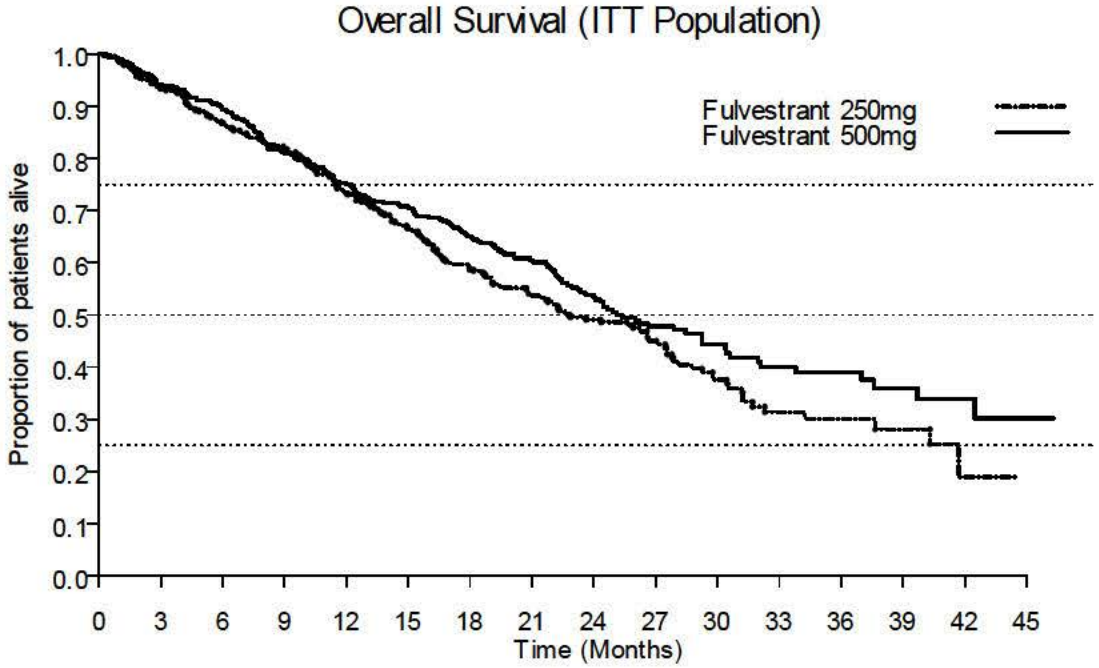


Figure 2: Kaplan-Meier OS: Study 1 ITT Population



Number at risk

Fulvestrant 250mg	374	344	314	293	260	233	194	140	107	72	51	30	18	11	3	
Fulvestrant 500mg	362	336	313	277	251	231	194	155	116	80	56	42	29	20	11	2

Comparison of FASLODEX 250 mg and Anastrozole 1 mg in Combined Data (Studies 2 and 3)

Efficacy of FASLODEX was established by comparison to the selective aromatase inhibitor anastrozole in two randomized, controlled clinical trials (one conducted in North America, Study 2; the other predominantly in Europe, Study 3) in postmenopausal women with locally advanced or metastatic breast cancer. All patients had progressed after previous therapy with an antiestrogen or progestin for breast cancer in the adjuvant or advanced disease setting.

The median age of study participants was 64. 81.6 % of patients had ER+ and/or PgR+ tumors. Patients with ER-/PgR- or unknown tumors were required to have demonstrated a prior response to endocrine therapy. Sites of metastases occurred as follows: visceral only 18.2%; viscera – liver involvement 23.0%; lung involvement 28.1%; bone only 19.7%; soft tissue only 5.2%; skin and soft tissue 18.7%.

In both trials, eligible patients with measurable and/or evaluable disease were randomized to receive either FASLODEX 250 mg intramuscularly once a month (28 days ± 3 days) or anastrozole 1 mg orally once a day. All patients were assessed monthly for the first three months and every three months thereafter. Study 2 was a double-blind, randomized trial in 400 postmenopausal women. Study 3 was an open-label, randomized trial conducted in 451 postmenopausal women. Patients on the FASLODEX arm of Study 2 received two separate injections (2 X 2.5 mL), whereas FASLODEX patients received a single injection (1 X 5 mL) in Study 3. In both trials, patients were initially randomized to a 125 mg per month dose as well, but interim analysis showed a very low response rate, and low dose groups were dropped.

Results of the trials, after a minimum follow-up duration of 14.6 months, are summarized in Table 5. The effectiveness of FASLODEX 250 mg was determined by comparing Objective Response Rate (ORR) and Time to Progression (TTP) results to anastrozole 1 mg, the active control. The two studies ruled out (by one-sided 97.7% confidence limit) inferiority of FASLODEX to anastrozole of 6.3% and 1.4% in terms of ORR. There was no statistically significant difference in overall survival (OS) between the two treatment groups after a follow-up duration of 28.2 months in Study 2 and 24.4 months in Study 3.

Table 5: Efficacy Results

	Study 2 (Double-Blind)		**Study 3 (Open-Label)**	
Endpoint	**FASLODEX 250 mg (n=206)**	**Anastrozole 1 mg (n=194)**	**FASLODEX 250 mg (n=222)**	**Anastrozole 1 mg (n=229)**
Objective tumor response				
Number (%) of subjects with CR[a] + PR[b]	35 (17.0)	33 (17.0)	45 (20.3)	34 (14.9)
% Difference in Tumor Response Rate (FAS[c] -ANA[d])	0.0		5.4	
2-sided 95.4% CI[e]	(-6.3, 8.9)		(-1.4, 14.8)	
Time to progression (TTP)				
Median TTP (days)	165	103	166	156
Hazard ratio[f]	0.9		1.0	
2-sided 95.4% CI[e]	(0.7, 1.1)		(0.8, 1.2)	

Stable Disease for ≥ 24 weeks (%)	26.7	19.1	24.3	30.1
Overall Survival (OS)				
Died n (%)	152 (73.8%)	149 (76.8%)	167 (75.2%)	173 (75.5%)
Median Survival (days)	844	913	803	736
Hazard Ratio[f]	0.98		0.97	
(2-sided 95% CI[e])	(0.78, 1.24)		(0.78, 1.21)	

[a]CR = Complete Response
[b]PR = Partial Response
[c]FAS = FASLODEX
[d]ANA = anastrozole
[e]CI = Confidence Interval
[f]Hazard ratio <1 favors FASLODEX

There are no efficacy data for the use of FASLODEX in premenopausal women with advanced breast cancer (women with functioning ovaries as evidenced by menstruation and/or premenopausal LH, FSH and estradiol levels).

16 HOW SUPPLIED/STORAGE AND HANDLING

FASLODEX is supplied in two different packaging configurations:

1. FASLODEX is supplied as two 5-mL clear neutral glass (Type 1) barrels, each containing 250 mg/5 mL of FASLODEX solution for intramuscular injection and fitted with a tamper evident closure.
   NDC 0310-0720-10

2. FASLODEX is supplied as one 5-mL clear neutral glass (Type 1) barrel containing 250 mg/5 mL of FASLODEX solution for intramuscular injection and fitted with a tamper evident closure.
   NDC 0310-0720-50

The syringes are presented in a tray with polystyrene plunger rod and safety needles (SafetyGlide™) for connection to the barrel.

Storage:
REFRIGERATE, 2°-8°C (36°-46°F). TO PROTECT FROM LIGHT, STORE IN THE ORIGINAL CARTON UNTIL TIME OF USE.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling

- **Pregnancy**
  Women of childbearing potential should be advised not to become pregnant while receiving FASLODEX. FASLODEX can cause fetal harm when administered to a pregnant woman *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)]*.

- **Blood Disorders**
  Because FASLODEX is administered intramuscularly, it should be used with caution in patients with bleeding disorders, decreased platelet count, or in patients receiving anticoagulants (for example, warfarin) *[see Warnings and Precautions (5.1)]*.

FDA-Approved Patient Labeling

PATIENT INFORMATION

FASLODEX® (faz-lo-dex)
(fulvestrant)

Read this Patient Information before you start receiving FASLODEX and before each injection. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is FASLODEX?

FASLODEX is a prescription medicine used to treat hormone receptor-positive breast cancer in women who have gone through menopause whose disease has spread after treatment with an antiestrogen medicine.

It is not known if FASLODEX is safe and effective in children.

Who should not receive FASLODEX?

You should not receive FASLODEX if you have had an allergic reaction to any of the ingredients in FASLODEX. See the end of this leaflet for a list of the ingredients in FASLODEX.

Symptoms of an allergic reaction to FASLODEX may include:
- itching
- swelling of your face, lips, tongue or throat
- trouble breathing

What should I tell my healthcare provider before taking FASLODEX?

Before you receive FASLODEX, tell your healthcare provider if you:

- have a low level of platelets in your blood or bleed easily.
- have liver problems
- have any other medical conditions
- are pregnant or plan to become pregnant. FASLODEX can harm your unborn baby. Talk to your healthcare provider about how to prevent pregnancy while taking FASLODEX. Tell your healthcare provider right away if you become pregnant or think you are pregnant while receiving FASLODEX.
- are breastfeeding or plan to breastfeed. You and your healthcare provider will decide if you will take FASLODEX or breast feed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. FASLODEX may affect the way other medicines work, and other medicines may affect how FASLODEX works.

Especially tell your healthcare provider if you take a blood thinner medicine.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider or pharmacist when you get a new medicine.

How will I receive FASLODEX?

Your healthcare provider will give you the appropriate amount of FASLODEX by injection into the muscle of your buttock.

What are the possible side effects of FASLODEX?

Common side effects of FASLODEX include:

- injection site pain
- nausea
- muscle, joint, and bone pain
- headache
- tiredness
- hot flashes
- vomiting
- loss of appetite
- weakness
- cough
- constipation
- shortness of breath
- increased liver enzymes

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects with FASLODEX. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to AstraZeneca at 1-800-236-9933.

General Information about FASLODEX.

Certain types of breast cancer require estrogen, a female hormone, to grow. FASLODEX works by blocking the effect of estrogen on certain tumors. This may slow the growth of tumors that are stimulated by estrogen.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. This leaflet summarizes the most important information about FASLODEX. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about FASLODEX that is written for health professionals.

For more information, go to www.FASLODEX.com

What are the ingredients in FASLODEX?

Active ingredient: fulvestrant

Inactive ingredients: alcohol, benzyl alcohol, benzyl benzoate, and castor oil.

SafetyGlide™ is a trademark of Becton Dickinson and Company.

FASLODEX is a trademark of the AstraZeneca group of companies.

Distributed by:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

Manufactured for:
AstraZeneca UK Limited
Macclesfield, Cheshire, England
By: Vetter Pharma-Fertigung GMBH & Co. KG
Ravensburg, Germany

Made in Germany

Rev. 09/10

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Pull Open Here

Twist Free

Both syringes must be administered to receive the 500 mg dose.

USUAL DOSAGE: See Prescribing Information for details of administration. See below for assembly instructions.

STORAGE: REFRIGERATE, 2–8°C (36–46°F). TO PROTECT FROM LIGHT, STORE IN THE ORIGINAL CARTON UNTIL TIME OF USE.

WARNING: As with all medications, keep out of the reach of children.

Carton contains: A total of 500 mg fulvestrant in TWO pre-filled syringes each containing 250 mg/5 mL (50 mg/mL), and two SafetyGlide™ shielding intramuscular injection needles.

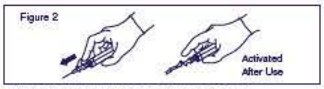
FASLODEX® also contains as inactive ingredients: Alcohol, USP; Benzyl Alcohol, NF; and Benzyl Benzoate, USP, as co-solvents; and Castor Oil, USP as a co-solvent and release rate modifier.

INSTRUCTIONS FOR INTRAMUSCULAR USE:

1. Remove glass syringe barrel from tray and check that it is not damaged.
2. Remove perforated patient record label from syringe.
3. Peel open the SafetyGlide™ outer packaging. For complete SafetyGlide™ instructions refer to prescribing information.
4. Break the seal of the white plastic cover on the syringe luer connector to remove the cover with the attached rubber tip cap *(see Figure)*.
5. Twist to lock the needle to the luer connector.
6. Remove needle sheath.
7. Remove excess gas from the syringe (a small gas bubble may remain).
8. Administer intramuscularly slowly in the buttock.
9. Immediately activate needle protection device upon withdrawal from patient by pushing lever arm completely forward until needle tip is fully covered *(see Figure 2)*.
10. Visually confirm that the lever arm has fully advanced and the needle tip is covered. If unable to activate, discard immediately into an approved sharps collector.
11. Repeat steps 1 through 10 for second syringe (both syringes must be administered to receive the 500 mg recommended dose).

Figure 1

Figure 2



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FASLODEX is a trademark of the AstraZeneca group of companies
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Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850
Manufactured for: AstraZeneca UK Ltd., Macclesfield, England
By: Vetter Pharma Fertigung GmbH & Co KG, Ravensburg, Germany
Made in Germany

AstraZeneca

FASLODEX® fulvestrant injection

250 mg/5 mL (50 mg/mL)

Both syringes must be administered to receive the 500 mg dose

OPEN HERE

NEW DOSING

FASLODEX® fulvestrant injection

250 mg/5 mL (50 mg/mL)

Both syringes must be administered to receive the 500 mg dose

LOT
EXP

(b)
(4)

FASLODEX® fulvestrant injection

250 mg/5 mL (50 mg/mL)

Both syringes must be administered to receive the 500 mg dose

For Single-Patient Use Only

FASLODEX®
fulvestrant injection

250 mg/5 mL (50 mg/mL)

For Intramuscular Use Only

NDC 0310 0720 10

This carton contains a total of 500 mg fulvestrant in TWO pre-filled syringes each containing 250 mg/5 mL (50 mg/mL), and two SafetyGlide™ shielding intramuscular injection needles.

Both syringes must be administered to receive the 500 mg dose.

REFRIGERATE, 2–8°C (36–46°F). TO PROTECT FROM LIGHT, STORE IN THE ORIGINAL CARTON UNTIL TIME OF USE.

Rx only

NEW DOSING

Contains **2** pre-filled syringes

AstraZeneca

FASLODEX® fulvestrant injection

250 mg/5 mL (50 mg/mL)

Both syringes must be administered to receive the 500 mg dose

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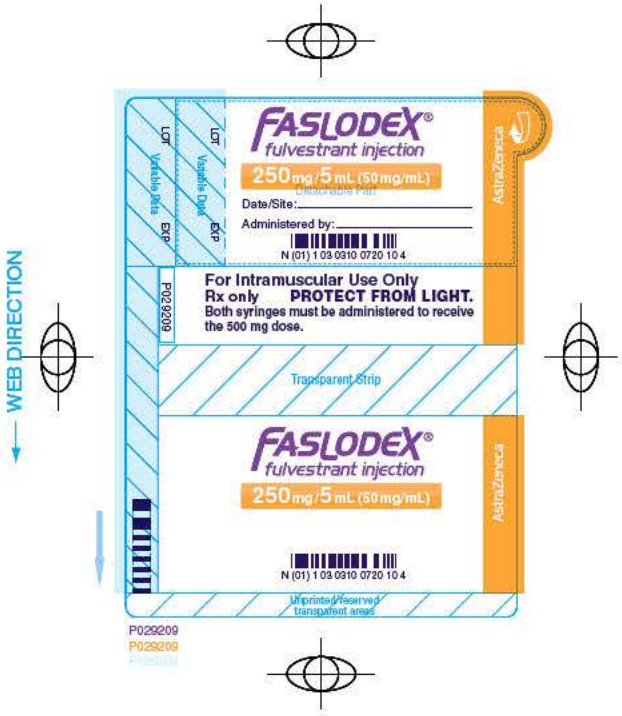

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s012

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	9/7/2010
From	Amna Ibrahim
Subject	Deputy Division Director Summary Review
NDA # **Supplement #**	21344 SE2-012
Applicant Name	AstraZeneca
Date of Submission	11/12/2009
PDUFA Goal Date	9/13/2010
Proprietary Name / **Established (USAN) Name**	FASLODEX® (fulvestrant) Injection Fulvestrant
Dosage Forms / Strength	Injection/ 50 mg/mL fulvestrant
Proposed Indication	Treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Tatiana Prowell MD/Amna Ibrahim MD
Statistical Review	Janet Jiang PhD/ Shenghui Tang PhD
Pharmacology Toxicology Review	Kimberly Ringgold PhD/ Haleh Saber PhD
CMC Review/OBP Review	Hamid Shafiei PhD/ Hasmukh Patel PhD
Microbiology Review	NA
Clinical Pharmacology Review	Young Jin Moon/Nitin Mehrotra/ Julie Bullock
DDMAC	Keith Olin/Stephanie Victor
DSI	NA
CDTL Review	This review will also serve as the CDTL review
OSE/DMEPA	Denise Baugh/Todd Bridges
OSE/DDRE	NA
OSE/DRISK	LaShawn Griffiths/Sharon R. Mills/Mary Willy

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction

This review is in lieu of the CDTL and DD review of NDA 21-344 for Faslodex®. Faslodex was initially approved for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy on 4/25/2002.

2. Background

This NDA submission supported a change in the dose of Faslodex for the existing indication. The indication remained unchanged. There was one major (CONFIRM) and two supportive studies from the clinical perspective (FINDER1 and FINDER2).

Per applicant, "*This application is based on a pivotal, randomised, double-blind, phase III study (Study D6997C00002 [CONFIRM]), comparing the proposed fulvestrant 500 mg dose regimen with the currently approved fulvestrant 250 mg regimen in 736 postmenopausal with oestrogen receptor positive (ER+ve), locally advanced or metastatic breast cancer, who entered the study having progressed or relapsed on an antioestrogen or an aromatase inhibitor."*

"The clinical programme for fulvestrant 500 mg also included 2 phase II studies (Studies D6997C00004 [FINDER1] and D6997C00006 [FINDER2]), which compared fulvestrant 500 mg and fulvestrant 250 mg treatment groups (92 and 93 patients in total in FINDER1 and FINDER2, respectively) in addition to a third fulvestrant 250 mg loading dose (fulvestrant 250 mg +LD) group. The FINDER studies also recruited ER+ve postmenopausal women with locally advanced or metastatic breast cancer, who had progressed or relapsed on an antioestrogen or an aromatase inhibitor."

"The FINDER studies were designed to assess potential ethnic differences between Japanese and Western patients in terms of the efficacy, PK and safety of 3 fulvestrant dose regimens. As the CONFIRM study was a phase III confirmatory study, adequately powered to investigate the difference between fulvestrant 500 mg and fulvestrant 250 mg, it is appropriate to draw overall efficacy conclusions based principally on CONFIRM."

3. CMC

I concur with the conclusions reached by the chemistry reviewer Hamid Shafiei, PhD in his review signed on 8/4/201, and cosigned by Hasmukh Patel PhD. Dr Shafei in his review states *"Based on the recommendations from the Pharm/Tox Reviewer and the Office of Compliance, and the review of the CMC information provided in this submission including specifications and the justification for specifications, "Description" and "How Supplied" section of the labeling, and the request for the categorical exclusion from the environmental assessment analysis, this supplement is recommended for approval from the CMC perspective."* The reviewer states *"For the inspection and evaluation of the proposed secondary packaging site*

an EES request was submitted to the Office of Compliance on 11/23/2009. The Office of Compliance on 11/25/2009 concluded that the proposed secondary packaging site is acceptable."

Manufacturing site inspections were acceptable. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer, Kimberly Ringgold PhD, cosigned by Haleh Saber PhD on 9/3/2010, that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer Young J Moon, PhD. In her review she states that there are no outstanding clinical pharmacology issues that preclude approval. Her review was cosigned by Nitin Mehrotra, PhD, Julie M. Bullock, Pharm D and Christine Garnett, Pharm D on 8/18/2010.

Two phase 2 trials (FINDER 1 and FINDER 2) were reviewed for the population pharmacokinetic analysis of fulvestrant, and one trial, a hepatic impairment study (Study 0063; Submission Date 12/1/05) was reviewed by Dr. Sophia Abraham (DARRTS communication date 2/26/07). Dr. Abraham stated in her review that a dose of 250 mg given once a month could be administered to patients with moderate hepatic impairment (Child-Pugh B), even though the mean AUC of fulvestrant increased by 70% compared to those with normal hepatic function. Dr Moon stated that the rationale for not reducing the dose at the time of this review in 2007 was because doses of 500 mg were safely being administered in ongoing clinical trials. She further states that since the current submission introduces a new dosing regimen (500 mg + additional dose at d15[AD]) and doses greater than 500 mg have not been tested in humans, the safety profile of the 500 mg + AD regimen is uncertain in patients with moderate hepatic impairment. Therefore, a 250 mg dose is recommended for patients with moderate hepatic impairment.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

A single trial (CONFIRM) provided the major support for this NDA. As noted by Dr Prowell (medical officer), the CONFIRM trial was a randomized, double-blind, controlled trial comparing two doses of Faslodex in 736 postmenopausal women with estrogen receptor-positive advanced breast cancer that had either recurred while on adjuvant endocrine therapy

or within 12 months of adjuvant endocrine therapy or had progressed on first endocrine therapy for advanced disease. Subjects were randomly assigned in a 1:1 ratio to receive either Faslodex 500 mg IM monthly + an additional 500 mg dose on day #14 of the first month of treatment or the approved dose of Faslodex 250 mg IM monthly. The primary endpoint of the study was progression-free survival (PFS) and overall survival (OS) and response rate (RR) were secondary endpoints. As eligibility criteria permitted, approximately one-third of study subjects did not have measurable disease at baseline. These subjects had either only bone metastases (20%) or bone metastases with additional non-measurable disease outside the bone (10%). Due to the double blind nature of the trial, an independent review of imaging studies was not required.

Figure 1: Study schema of the CONFIRM trial
Applicant's figure

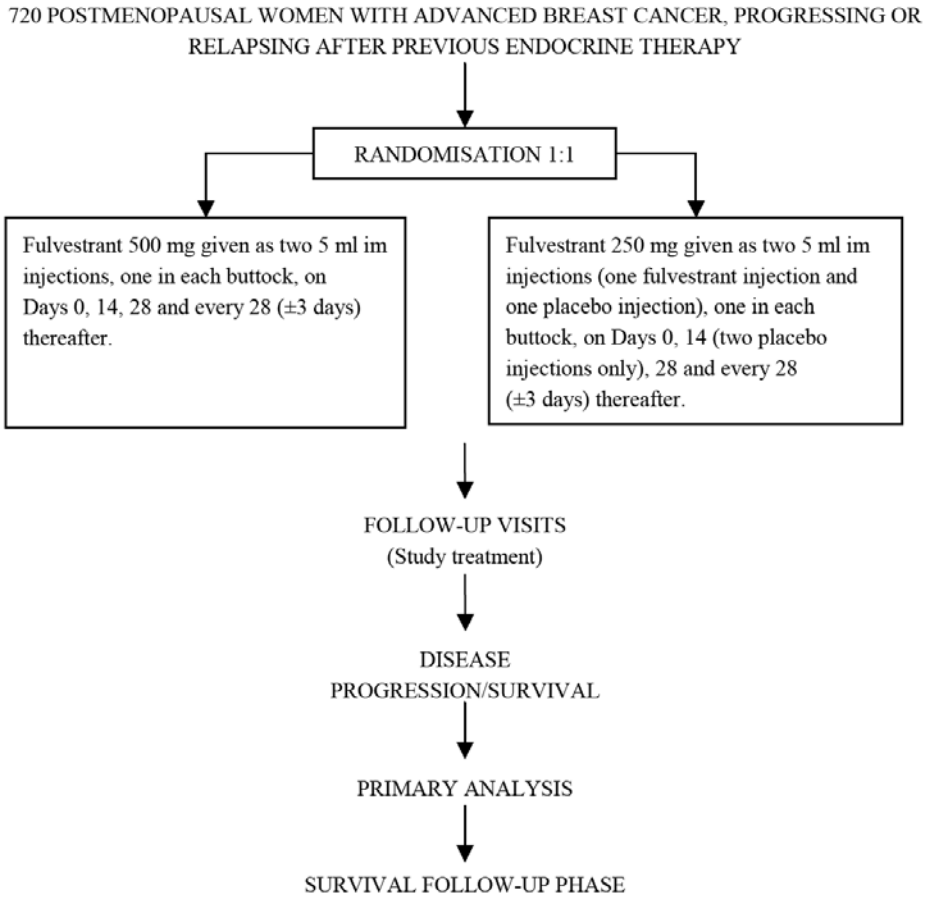


Table 1: Efficacy Results

	Fulvestrant 500 mg (N=362)	Fulvestrant 250 mg (N=374)
PFS Median (months)	6.5	5.4
Hazard Ratio (95% CI)	0.80 (0.68–0.94)	
p-value	0.006	
OS Died	175 (48.3)	203 (54.3)
Median OS (months)	25.1	22.8
Hazard Ratio (95% CI)	0.84 (0.69–1.03)	
ORR (95% CI)	13.8% (9.7%, 18.8%) (33/240)	14.6% (10.5%, 19.4%) (38/261)

PFS (Progression Free Survival) = the time between randomization and the earliest of progression or death from any cause.
Hazard ratio < 1 favors FASLODEX 500 mg.
CI = Confidence Interval
OS = Overall Survival
ORR (Objective Response Rate), was analyzed in the evaluable patients with measurable disease at baseline (fulvestrant 500 mg N=240; fulvestrant 250 mg N=261).

Figure 2: Kaplan Meier Curve for PFS

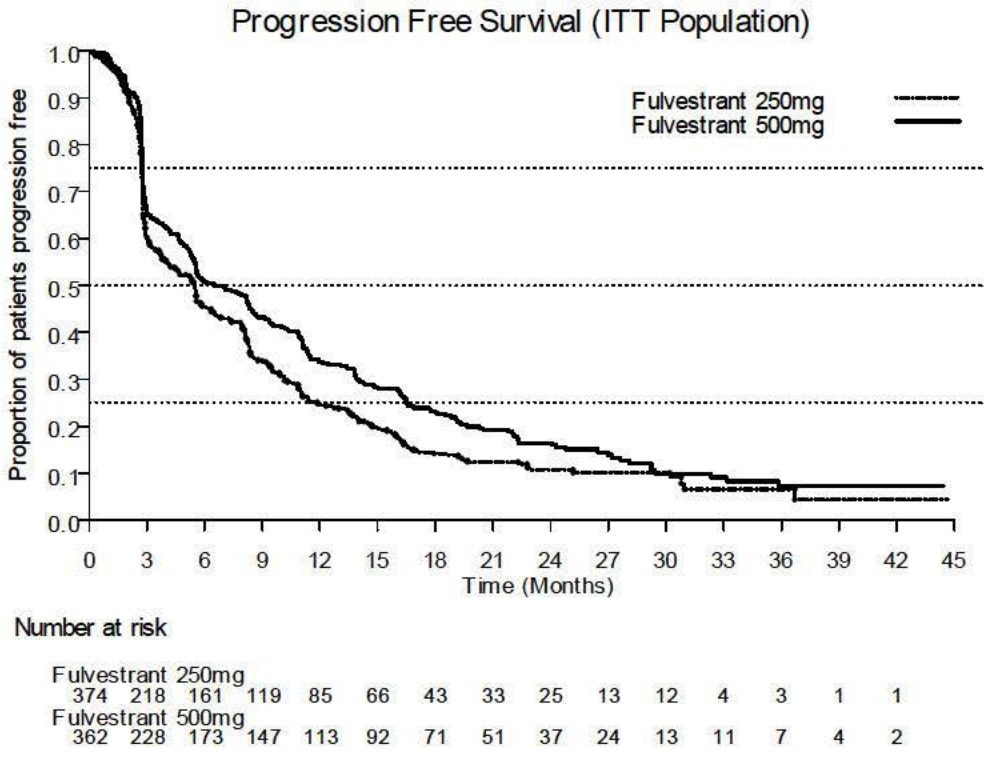
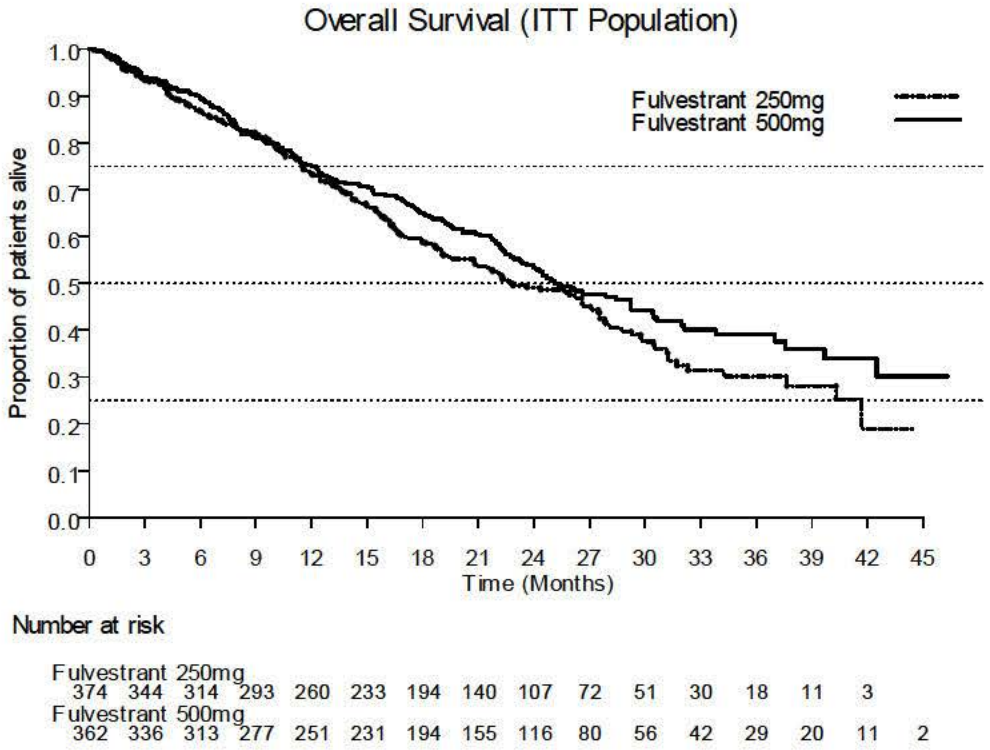


Figure 3: Kaplan Meier Curve for Overall Survival



Multiple sensitivity analyses were performed, including PFS in patients with non-measurable disease and PFS in patients in whom disease progression was not confirmed or not confirmed by unacceptable imaging modality. The results of these analyses were consistent with the primary analysis and hazard ratio as less than 1. Please see statistical review for details.

In the 'Conclusions and Recommendations' section of her review, the statistical reviewer Xiaoping Jiang PhD states that *"The results from the pivotal study D6997C00002 demonstrated that the fulvestrant 500 mg had statistically significant improvement of progression free survival (PFS) compared to the currently approved dose of fulvestrant 250 mg"* and continues to state that *"Whether the magnitude of 1.1 months improvement in median PFS with HR of 0.80 (95% CI: 0.68; 0.94) with no advantage in overall survival or objective response rate can be considered a sufficient evidence of clinical benefit to support approval of 500 mg dosage of fulvestrant in the replacement of currently approved dosage will depend on the favorable risk-benefit ratio and be deferred to the clinical team."* The statistics review was cosigned by Shenghui Tang PhD and Rajeshwari Sridhara PhD.

8. Safety

Per Dr Prowell, there were 735 patients who received a first dose of fulvestrant in the CONFIRM trial and constitute the primary safety population analyzed in this sNDA. Of these, 361 were treated on the fulvestrant 500 mg arm. Pooled safety data using the CONFIRM,

NEWEST, FINDER 1, and FINDER 2 trials, all of which included arms comparing fulvestrant 500 mg to fulvestrant 250 mg monthly, were also examined for certain key safety outcomes. The pooled safety population included 1,127 subjects, of whom 567 were fulvestrant 500 mg. The pooled safety data from the CONFIRM, NEWEST, FINDER 1 and FINDER 2 trials (N=1127) demonstrated no clinically significant difference in the overall incidence of any grade AEs, grade ≥ 3 AEs, serious adverse events, deaths on study, or AEs leading to discontinuation of treatment in subjects treated with fulvestrant 500 mg monthly compared with those who received 250 mg monthly.

9. Advisory Committee Meeting

NA

10. Pediatrics

A pediatric waiver was requested and granted as breast cancer does not occur in children.

11. Other Relevant Regulatory Issues

- DSI Audits: not done
- Financial Disclosure: No financial relationships likely to have impacted the conduct or findings of the trial were disclosed for any of the investigators listed on the form 3454.
- DDMAC: Comments were reviewed, discussed with DDMAC and incorporated as applicable.

There are no other unresolved relevant regulatory issues

12. Labeling

- Proprietary name: the indication or name of the drug did not require any change

- Physician labeling: all major labeling issues have been resolved.

  Labeling issues were captured well by Dr Prowell. She states in her review that *"the clinical team recommended to the Sponsor* (b) (4)

(b) (4)

(b) (4)

(b) (4) *These labeling recommendations were discussed by the review team and the Sponsor in a teleconference on 07/26/2010,* (b) (4)

FDA concluded that the Sponsor's request to approve a single labeled dose of 500 mg monthly with an additional dose of 500 mg on day #14 was acceptable"

"Per clinical pharmacology, a dose of 250 mg monthly with (b) (4) *an additional 250 mg dose on day #15 of the first cycle was recommended for patients with moderate hepatic impairment (Child-Pugh Class B). There are no data to support the safe use of fulvestrant in patients with severe hepatic impairment (Child-Pugh Class C)."*

"The labeling should be updated to communicate that liver function abnormalities, which are generally grade 1 or 2 elevations in transaminases or alkaline phosphatase, occur in approximately 15% of patients in association with fulvestrant use. Grade ≥ 3 abnormalities of liver function occur in up to 2% of subjects. These liver function abnormalities do not demonstrate dose-dependence"

"The labeling should be updated to recommend that fulvestrant be used with caution in patients who are receiving anticoagulants or who have thrombocytopenia rather than stating that the fulvestrant is contraindicated, comparable to the EMA-approved labeling of fulvestrant. A Pubmed search by this reviewer identified no case reports of bleeding complications following treatment with fulvestrant in patients with thrombocytopenia or anticoagulant use despite a theoretical increase in risk of bleeding for such patients."

- Carton and immediate container labels; Comments from DMEPA reviewers were sent to the sponsor and were addressed. In an email dated 8/26/2010, Denise Baugh stated that the container label, carton labeling and insert labeling are all acceptable.

- Patient labeling/Medication guide: Appropriate changes were made to the patients labeling. There was no medication guide

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment
  No discipline recommends a Complete Response letter. Biometrics discipline states "*Whether the magnitude of 1.1 months improvement in median PFS with HR of 0.80 (95% CI: 0.68; 0.94) with no advantage in overall survival or objective response rate can be considered a sufficient evidence of clinical benefit to support approval of 500*

mg dosage of fulvestrant in the replacement of currently approved dosage will depend on the favorable risk-benefit ratio and be deferred to the clinical team."

I concur with the medical officer's assessment. Dr Prowell recommends approval of this supplement. She states *"This trial demonstrated a statistically significant improvement in progression-free survival (PFS) with a HR of 0.80 (95% CI 0.68, 0.94, p=0.006). This corresponded to a 1.1 month improvement in median PFS [6.5 months (95% CI 5.5, 8.4) versus 5.4 months (95% CI 4.0, 6.3)] for the fulvestrant 500 mg and 250 mg arms, respectively. Supportive of the primary endpoint was a trend for improvement in overall survival (OS) with a HR of 0.84 (p=0.09, unadjusted for multiplicity), favoring the fulvestrant 500 mg monthly regimen. There was no meaningful difference in overall or grade $\geq$ 3 toxicity between the two arms."*

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  None required.

- Recommendation for other Postmarketing Requirements and Commitments
  There are no unfulfilled PMCs. No new ones are recommended.

Amna Ibrahim MD
Deputy Division Director

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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

/s/

AMNA IBRAHIM
09/07/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s012

OFFICER/EMPLOYEE LIST

List of Employees associated with this action:

Amna Ibrahim
Tatiana Prowell
Julie Bullock
Young-Jin Moon
Nitin Mehrotra
Christine Garnett
Hamid Shafiei
Hasmukah Patel
Shenghui Tang
Xiaoping Janet J Jiang
Kun He
Rajesiwari Sridhara
Denise Miller
Stephen Langille
Sharon Mills
Mary Willy
Denise Baugh
Todd Bridges
Kellie Taylor
Keith Olin
Stephanie Victor
Haleh Saber
Kimberly Ringgold

CENTER FOR DRUG EVALUATION AND RESEARCH

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s012

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Supplemental NDA
Application Number(s)	21-344
Priority or Standard	Standard
Submit Date(s)	11/13/2009
Received Date(s)	11/14/2009
PDUFA Goal Date	09/13/2010
Division / Office	OODP/DDOP
Reviewer Name(s)	Tatiana (Tanya) M. Prowell
Review Completion Date	08/12/2010
Established Name	Fulvestrant
(Proposed) Trade Name	Faslodex
Therapeutic Class	Anti-estrogen
Applicant	AstraZeneca
Formulation(s)	Injection
Dosing Regimen	(b) (4)
Indication(s)	(b) (4) HR+ breast cancer, following failure of an anti-estrogen
Intended Population(s)	Postmenopausal women with (b) (4) HR+ breast cancer

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical team recommends approval of the supplemental new drug application (sNDA) for Faslodex 500 mg IM monthly with an additional 500 mg IM loading dose on day #14 for treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy. The recommendation for approval is based upon the results of a randomized, double-blind, placebo-controlled trial (CONFIRM), which compared fulvestrant 250 mg IM monthly to fulvestrant 500 mg IM monthly with an additional 500 mg loading dose on day #14 of cycle 1. This trial demonstrated a statistically significant improvement in progression-free survival (PFS) with a HR of 0.80 (p=0.006) and a trend for an improvement in overall survival (OS) with a HR of 0.84 (p=0.09, unadjusted for multiplicity), favoring the fulvestrant 500 mg monthly regimen, with no meaningful increase in common or serious adverse events.

1.2 Risk Benefit Assessment

The foundation of the sNDA submission was the CONFIRM trial, a randomized controlled trial comparing two doses of Faslodex in 736 postmenopausal women with estrogen receptor-positive advanced breast cancer that had either recurred while on adjuvant endocrine therapy or within 12 months of adjuvant endocrine therapy or had progressed on first endocrine therapy for advanced disease. Subjects were randomly assigned in a 1:1 ratio to receive either Faslodex 500 mg IM monthly + an additional 500 mg dose on day #14 of the first month of treatment or the approved dose of Faslodex 250 mg IM monthly.

This trial demonstrated a statistically significant improvement in progression-free survival (PFS) with a HR of 0.80 (95% CI 0.68, 0.94, p=0.006). This corresponded to a 1.1 month improvement in median PFS [6.5 months (95% CI 5.5, 8.4) versus 5.4 months (95% CI 4.0, 6.3)] for the fulvestrant 500 mg and 250 mg arms, respectively. Supportive of the primary endpoint was a trend for improvement in overall survival (OS) with a HR of 0.84 (p=0.09, unadjusted for multiplicity), favoring the fulvestrant 500 mg monthly regimen. There was no meaningful difference in overall or grade $\geq$ 3 toxicity between the two arms.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No additional postmarketing risk evaluation and mitigation strategies are being recommended. Note that Faslodex is already marketed at the 250 mg IM monthly dose for advanced breast cancer.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarketing requirements or commitments are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Established name: Faslodex

Faslodex (fulvestrant) is a pure estrogen receptor antagonist administered via intramuscular injection. It is approved in the United States for the following indication:

- For treatment of hormone receptor-positive (HR+) metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy, at a dose of 250 mg IM once a month.

This submission is an efficacy supplement to modify the recommended dosing for the following indication:

- For treatment of hormone receptor-positive (HR+) metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy, at a dose of 500 mg IM once a month with an additional 500 mg dose given two weeks after the initial dose.

2.2 Tables of Currently Available Treatments for Proposed Indications

Note that other cytotoxics are available for treatment of metastatic breast cancer such as mitomycin and vinblastine and have indeed served as control arms in previous pivotal trials; these agents have been omitted from the table due to the rarity of their use in the United States.

Table 1: Available Therapy for Advanced Breast Cancer in the U.S.

Available Therapy for All Patients	
Paclitaxel	Docetaxel†
Cyclosphosphamide, methotrexate, fluorouracil (CMF)	Capecitabine†
Vinorelbine	Bevacizumab/paclitaxel
Gemcitabine	Ixabepilone
Hormone Receptor + Subset Only	
Tamoxifen	Letrozole
Anastrozole	Exemestane

†Note: Except where indicated, cytotoxics for metastatic breast cancer are most often used as sequential monotherapy rather than combination therapy.

2.3 Availability of Proposed Active Ingredient in the United States

Faslodex (fulvestrant) is already approved and marketed in the United States for the same indication at a dose of 250 mg IM monthly.

2.4 Important Safety Issues with Consideration to Related Drugs

Faslodex (Faslodex) is a marketed drug in the United States for advanced breast cancer in postmenopausal women. As reflected in current product labeling, Faslodex may theoretically result in bleeding complications in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use due to intramuscular route of administration. The most frequent adverse events associated with fulvestrant use include gastrointestinal symptoms (nausea, vomiting, diarrhea, constipation, and abdominal pain), headache, back pain, hot flashes, pharyngitis, and musculoskeletal complaints. In addition, fulvestrant may cause an increase in hepatic transaminases which is generally low-grade and self-limited, even with continuation of fulvestrant.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

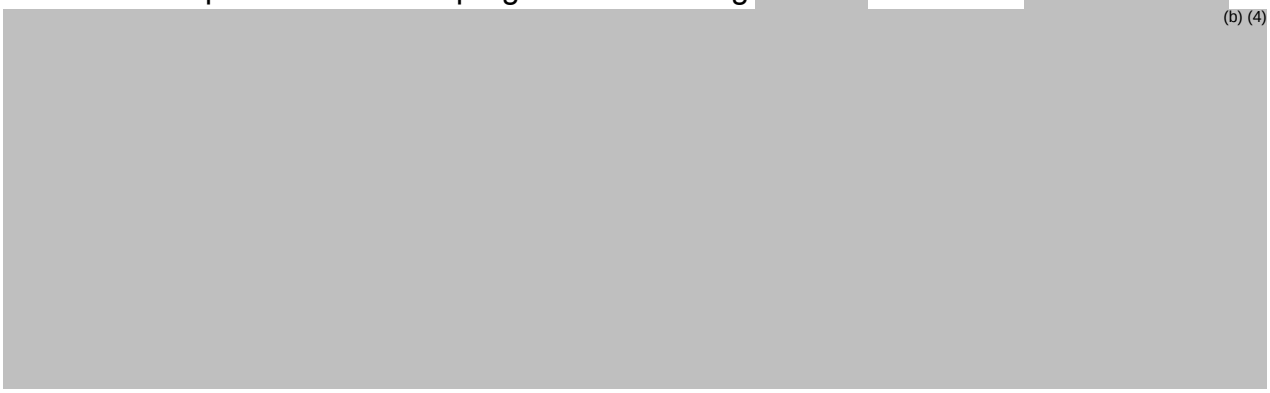
Faslodex was originally approved in 2002 in the United States for treatment of HR+ metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy (i.e. tamoxifen).

The phase 3 randomized trial submitted in support of the current supplement (CONFIRM trial) was conducted as a post-marketing requirement (dose comparison efficacy and safety trial) of the European Medicines Agency (EMA) following marketing

approval in the EU. The protocol was never submitted for special protocol assessment in the U.S.

Pre-NDA meeting: A pre-NDA meeting was held on October 1, 2009. The Sponsor asked whether the results of the CONFIRM study design were adequate to support a sNDA submission to change the currently approved dose of fulvestrant from 250 mg monthly to 500 mg monthly. FDA agreed that the data would support submission of the sNDA, but cautioned the Sponsor that the improvement in the primary endpoint was modest.

AstraZeneca also asked whether the CONFIRM trial, which was amended to permit enrollment of patients who had progressed following (b) (4) tamoxifen (b) (4)



2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The sNDA submission was generally well-organized and complete other than the narratives provided by the Sponsor. The narratives were simple listings of adverse events, concomitant medications, and causality assessments with a brief area for comments that was often blank. The lack of true narratives limited this reviewer's ability to assess the circumstances of deaths preceded by an adverse event, though deaths on treatment were relatively uncommon.

3.2 Compliance with Good Clinical Practices

The study protocol and amendments were reviewed by an Institutional Review Board or Independent Ethics Committee. The sponsor affirms that all studies described in the submission were conducted in accordance with Good Clinical Practice. All subjects were to provide written informed consent prior to study enrollment.

No Division of Scientific Investigations (DSI) audit was felt to be necessary for this supplemental NDA in support of a dose change.

3.3 Financial Disclosures

No financial relationships likely to have impacted the conduct or findings of the trial were disclosed for any of the investigators listed on the form 3454.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

No new chemistry manufacturing and controls (CMC), clinical microbiology, or preclinical pharmacology/toxicology (PT) data were submitted in support of this sNDA.

4.1 Chemistry Manufacturing and Controls

Not applicable. No new chemistry manufacturing and controls (CMC) data were submitted for review.

4.2 Clinical Microbiology

Not applicable. No new clinical microbiology data were submitted for review.

4.3 Preclinical Pharmacology/Toxicology

Not applicable. No new pharmacology/toxicology (P/T) data were submitted for review.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

From the existing product label:

"Fulvestrant is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner with affinity comparable to that of estradiol. Fulvestrant downregulates the ER protein in human breast cancer cells."

4.4.2 Pharmacodynamics

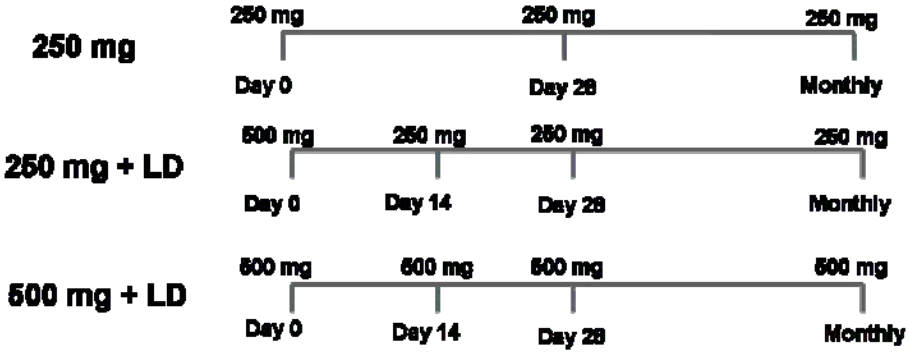
Not applicable.

4.4.3 Pharmacokinetics

Section 4.4.3 is modified from the reviews of Young-Jin Moon and Nitin Mehotra, reviewers in Clinical Pharmacology and Pharmacometrics.

Two phase 2 studies D6997C0004 (FINDER1) and D6997C0006 (FINDER2) in 143 Japanese patients and 144 Caucasian patients with estrogen receptor positive advanced breast cancer progressing or relapsing after previous endocrine therapy assessed the pharmacokinetics (PK) of fulvestrant in patients treated with fulvestrant 250 mg, 250 mg + loading dose (LD) regimen, and 500 mg + LD. The doses and schedules compared in these studies are shown below in Figure 1.

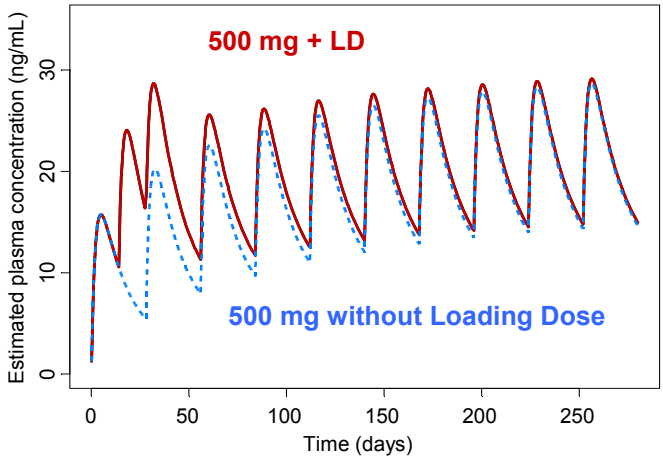
Figure 1: Dosing regimen for the FINDER1 and FINDER2 Trials



Mean values [CV] of AUC, Cmax and Cmin at Month 1 were 475 (31.1%) ng·days/mL, 25.2 (32.8%) ng/mL, 16.3 (24.6%) ng/mL, respectively.

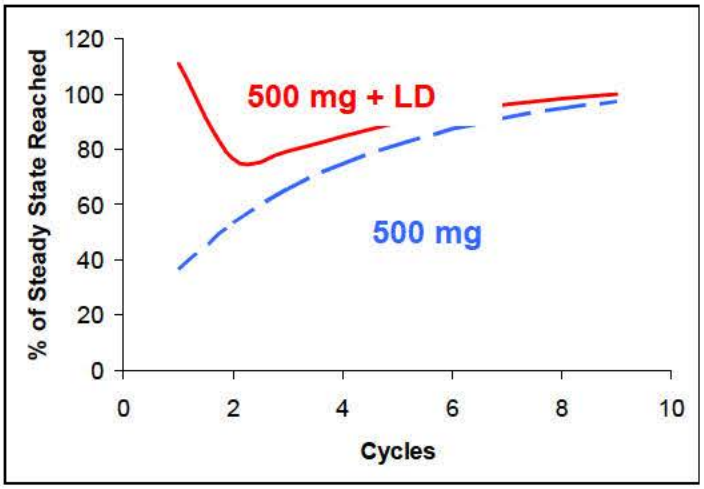
The addition of a loading dose at Day 14 causes plasma concentrations of fulvestrant to approximate steady state levels within the first month of dosing. The mean plasma concentration profiles for a 70 kg patient after 500 mg + LD and 500 mg without LD were predicted based on the parameter estimates obtained from the population pharmacokinetic model. Eventually similar steady state levels are achieved with these two dosing regimens. However, for the first two months, the 500 mg + LD regimen results in higher exposures (closer to steady state exposures) compared to the 500 mg without LD regimen. Predicted data are shown in Figure 2 below. Note the early separation of the plasma concentration curves, which are superimposed in later cycles.

Figure 2: Predicted Mean Plasma Concentration Profiles for a 70 kg Individual after Monthly Doses of 500 mg + LD (red) and 500 mg without LD (blue)



The above result was also expressed by % of steady state reached at each cycle. Based upon the half-life of fulvestrant (~40 days), steady state would be reached at cycle 9. Percent of steady state reached was calculated by trough concentration at each cycle divided by trough concentration at cycle 9. As shown in Figure 3, inclusion of a loading dose two weeks after the initial dose produces concentrations that approximate steady state levels within one month of dosing.

Figure 3: Percentage of Steady State Concentration by Cycle



The oral clearance and volume of distribution did not depend on age, body mass index, ideal body weight, dose, or race.

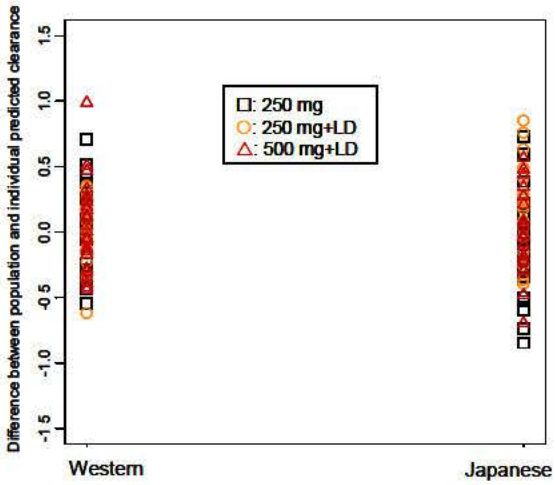
As shown in Table 2, the median PFS of the Western population receiving 250 mg of fulvestrant was much lower than that of the same population receiving either 250 mg + LD or 500 mg + LD, whereas no significant difference was observed in PFS among the Japanese population receiving the various dosing regimens.

Table 2: Summary of Median PFS (mos) in FINDER1 and FINDER2 Trials

	250 mg	250 mg + LD	500 mg + LD
Western (N=144)	3.1 (N=47)	6.1 (N=51)	6.0 (N=46)
Japanese (N=143)	6.0 (N=45)	7.5 (N=51)	6.0 (N=47)

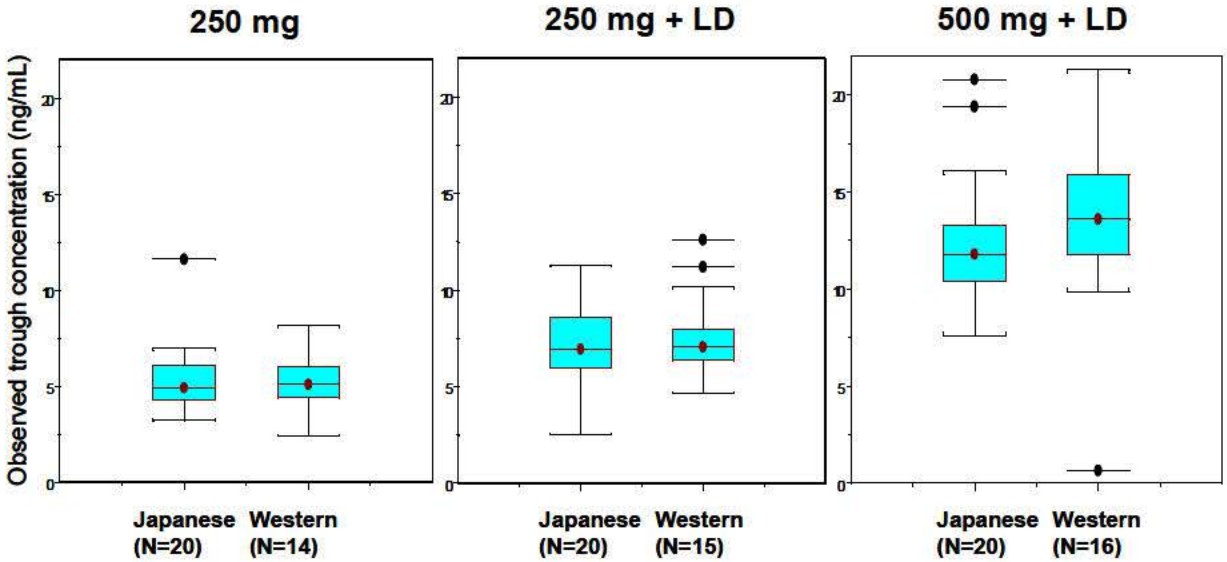
Differences between population and individual predicted clearance from the final population PK model were compared between Japanese and Western patients to determine if the observed difference in PFS may be attributable to ethnic pharmacokinetic differences. As shown in Figure 4, there was no difference observed in clearance of fulvestrant between Japanese and western patients.

Figure 4: Population and Individual Predicted Clearance for Western and Japanese Patients



There was also no significant difference in observed trough concentrations between Japanese and Western patients following three different doses at Month 3, as is shown in Figure 5 below.

Figure 5: Observed Trough Concentrations (ng/mL) in Japanese and Western Patients at 250 mg, 250 mg + LD, and 500 mg + LD



5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The tabular listing of studies is taken from the Sponsor's Clinical Study Report Section 5.2.

Table 3: Faslodex Clinical Studies (Sponsor's Table)

1. TABULAR LISTING OF CLINICAL STUDIES

Type of study	Study identifier	Location of study report in Module 5	Primary objective of the study[a]	Study design and type of control	Test product(s), Dosage regimen, Route of administration	No. of patients randomised/ treated	Patient population	Duration of treatment	Study status; type of report
Efficacy and tolerability	CONFIRM (D6997C00002) including CONFIRM addendum[b]	5.3.5.1	To compare the efficacy of fulvestrant 500 mg treatment with fulvestrant 250 mg treatment in terms of time to progression (TTP).	Randomised, double-blind, parallel-group	Fulvestrant 500 mg intramuscularly (im) every 28 (±3) days plus an additional 500 mg on Day 14 (±3) of first month only **vs.** fulvestrant 250 mg im every 28 (±3) days	736 patients were randomised. 361 received fulvestrant 500 mg and 374 received fulvestrant 250 mg	Postmenopausal women with histological/ cytological confirmation of ER+ve breast cancer who had relapsed or progressed on previous endocrine therapy.	Treatment was to continue until disease progression occurred, unless any of the criteria for treatment discontinuation were met first.	Complete; full including addendum
Efficacy and tolerability	FINDER1 (D6997C00004)[c] including FINDER1 addendum[d]	5.3.5.1	To evaluate the objective response rate (ORR) of patients treated with fulvestrant 250 mg, fulvestrant 250 mg (plus 250 mg loading regimen) and fulvestrant 500 mg.	Randomised, double-blind, parallel-group	See Figure 1 (Route: im)	143 patients were randomised. 46 received fulvestrant 500 mg, 51 received fulvestrant 250 mg +LD and 45 received fulvestrant 250 mg	Postmenopausal women with ER+ve advanced breast cancer who had either: relapsed whilst on adjuvant endocrine therapy; or progressed whilst on first endocrine therapy for advanced disease; or who had recurrent disease within 12 months after completion of adjuvant therapy.	Treatment was to continue until disease progression occurred, unless any of the criteria for treatment discontinuation were met first.	Complete; full including addendum
Efficacy and tolerability	FINDER2 (D6997C00006)[c] including FINDER2 addendum[d]	5.3.5.1	To evaluate the objective response rate (ORR) of patients treated with fulvestrant 250 mg, fulvestrant 250 mg (plus 250 mg loading regimen) and fulvestrant 500 mg.	Randomised, double-blind, parallel-group	See Figure 1	144 patients were randomised. 46 received fulvestrant 500 mg, 50 received fulvestrant 250 mg +LD and 47 received fulvestrant 250 mg	Postmenopausal women with ER+ve advanced breast cancer who had either: relapsed whilst on adjuvant endocrine therapy; or progressed whilst on first endocrine therapy for advanced disease; or who had recurrent disease within 12 months after completion of adjuvant therapy.	Treatment was to continue until disease progression occurred, unless any of the criteria for treatment discontinuation were met first.	Complete; full including addendum

Efficacy and tolerability	NEWEST (D6997C00003)[c,e]	5.3.5.4	To compare the effects of fulvestrant 500 mg and fulvestrant 250 mg on the proliferation marker Ki67 after 4 weeks of treatment.	Randomised, open-label	Fulvestrant 500 mg on Days 0, 14, 28, 56, and 84 **vs.** fulvestrant 250 mg on Days 0, 28, 56, and 84. (At the completion of 16 weeks of treatment, patients underwent definitive surgery.)	211 patients were randomised. 108 received fulvestrant 500 mg and 100 received fulvestrant 250 mg[f]	Women with histologically or cytologically confirmed invasive ER+ breast cancer who were postmenopausal. Tumors had to be newly diagnosed and either operable or potentially operable depending on the degree of advancement; the largest tumor diameter had to measure at least 2 cm.	Treatment was to continue for 16 weeks with an 8 additional weeks of fulvestrant therapy (as randomised) if the investigator believed that further benefit could be achieved prior to surgery.	Complete; full

a For secondary and exploratory objectives see study report in Module 5.
b CONFIRM CSR addendum to report FDA requested analysis of TTP.
c FINDER1 and FINDER2 incorporated population PK: C_{max}, clearance and volume of distribution at steady state. NEWEST incorporated PK and PK/PD objectives; the latter examined the effects of fulvestrant on the proliferation marker Ki67.
d Addenda of safety narratives for patients who died due to progression during the study treatment period but had not experienced an SAE or an AE leading to discontinuation. Safety narratives for all patients who died due to an AE, experienced an SAE or discontinued due to an AE during the treatment period were included in the main CSR.
e The safety data from NEWEST were included in the safety evaluation (pooled analysis) owing to there being a fulvestrant 250 mg group comparator to provide an intra-study safety comparison. However, the efficacy data were not included in the efficacy comparison owing to differences between NEWEST and the CONFIRM, FINDER1 and FINDER2 studies in terms of the study population and treatment duration (see above).
f One patient (E3002004) in the fulvestrant 500 mg group was actually treated at the 250 mg dosage.
g FIRST was from the safety evaluation (pooled analysis) owing to there being no fulvestrant 250 mg group comparator to provide an intra-study safety comparison, which would have introduced the possibility of bias in the fulvestrant 500 mg versus 250 mg comparison. However, the safety data for FIRST are provided separately to the pooled data in the Summary of Clinical Safety. FIRST was excluded form the efficacy comparison owing to differences between FIRST and the CONFIRM, FINDER1 and FINDER2 studies in terms of the study population and treatment duration (see above).

5.2 Review Strategy

The review of this sNDA was conducted by a single clinical reviewer. The primary assessment of the efficacy and safety of fulvestrant at the proposed 500 mg IM monthly dose is derived from the original submission and 4 month Safety Update of the CONFIRM trial and arms of the FINDER1 and 2 trials relevant to the proposed indication.

The primary review activities for this sNDA included:

- Review of pre-NDA package and participation in pre-NDA internal/Sponsor meetings
- Review of the electronic submission of the original sNDA and 4-month safety update;
- Review of Sponsor electronic submissions in response to FDA clinical queries;
- Reproduction and/or auditing of key efficacy and safety analyses with JMP using raw datasets provided by the applicant.
- Reading and incorporation of reviews written by fulvestrant reviewers from other disciplines

It is of note that Faslodex has been approved and marketed in the United States at the lower dose of 250 mg IM monthly for the same patient population since 2002 and generally has a well-established toxicity profile, though the adverse event profile may

change when given at a higher dose. The pivotal trial submitted to the sNDA comparing the currently approved dose to the new dosing regimen sought by the Sponsor is the CONFIRM trial. In addition, the FINDER 1 and FINDER 2 trials were submitted by the Sponsor as supportive efficacy and safety data and are discussed in Section 5.3. Details of the trial design, demographics, etc. for the CONFIRM trial may be found in Section 6.1 and are briefly described below.

The CONFIRM trial was a randomized, multinational, double-blind, parallel-group phase 3 study that compared two dosing regimens for fulvestrant—the approved 250 mg IM monthly regimen plus an additional monthly placebo injection versus 500 mg IM monthly with an additional 500 mg loading dose (LD) on day #14 of the first cycle--in 736 postmenopausal women with ER+ advanced breast cancer who had either relapsed while on or within 12 months of adjuvant endocrine therapy, or progressed while on first endocrine therapy for advanced disease. An amendment (Amendment #1) to the trial permitted enrollment of patients who had received an aromatase inhibitor (AI) as their last prior hormonal therapy. The primary endpoint was termed time to progression (TTP) by the Sponsor, but was defined as disease progression or death due to any cause, and therefore is usually termed progression-free survival (PFS). For the sake of convention, this review will refer to the primary endpoint as PFS.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 CONFIRM Trial

The phase 3 trial supporting this supplemental NDA was the CONFIRM trial. This trial is discussed in detail in Section 6.1.1.

5.3.2 FINDER 1 Trial

The FINDER 1 trial was a randomized, double-blind, parallel-group trial comparing three dosing regimens--fulvestrant 250 mg IM every 28 days, fulvestrant 500 mg IM every 28 days with an additional 500 mg IM dose on d#14 of cycle 1, and fulvestrant 500 mg IM on d#0 with 250 mg IM on d#14, d#28 and every 28 days thereafter—in 143 postmenopausal women with HR+ advanced breast cancer who relapsed on endocrine therapy, progressed while on first endocrine therapy for advanced disease, or had disease recurrence within 12 months after completion of adjuvant therapy. Measurable disease was required. The trial was conducted exclusively in Japan. The primary endpoint was objective response rate (RR). Note that the third arm, which combined a 500 mg IM loading dose on day zero with the 250 mg IM dosing regimen, will not be discussed further given the lack of relevance to the proposed dose change for this sNDA.

In the FINDER 1 trial, there were 4 patients (9%) [95% CI 6.3-28.9%] who responded in the fulvestrant 250 mg arm compared with 7 patients (15%) [95% CI 2.4-20.4%] who responded in the 500 mg arm. This difference was not statistically significant. The TTP was approximately doubled in the 500 mg arm (6.0 months vs. 3.1 months). It is noteworthy that the TTP of 3.1 months in the control arm is much lower than would be expected based upon historical data as well as other RCT data submitted in the current sNDA and lower than the estimated TTP for this population (5.7 months) used to select the sample size for the CONFIRM trial.

5.3.2 FINDER 2 Trial

The FINDER 2 trial, which randomized a total of 144 patients, was of identical design to FINDER 1, but was conducted in North America and Europe. There were 5 patients with an objective response in each arm (11%). The TTP was identical in the two arms at (6 months).

The review team did consider the possibility that the difference in the TTP results of the FINDER 1 and 2 trials was a result of pharmacokinetics given the differing patient populations (Asian versus European origin). The clinical pharmacology reviewers were asked to review the available pharmacokinetic data to determine whether the decreased TTP in the FINDER 1 population who received the 250 mg regimen may have been due to decreased drug exposure in this population relative to the FINDER 2 population receiving the same dose. This did not appear to be the case. These findings are discussed in further detail in Section 4.4.

Reviewer Note: In the CONFIRM trial, there was a greater improvement in median PFS in the subpopulation of patients with non-measurable disease at baseline (i.e. predominantly patients with isolated skeletal metastases) than in those patients with measurable disease at baseline (i.e. generally visceral involvement). Given that the FINDER 2 required measurable disease at entry because of the primary endpoint (overall response rate), the lack of a statistically significant improvement in TTP in FINDER 2 may be viewed as consistent with the results of the CONFIRM trial. This may be explained by the relative endocrine resistance often observed in hormone receptor-positive breast cancers that have metastasized to the viscera.

5.3.3 Other Trials

Two additional trials were submitted by the Sponsor and have been briefly reviewed but will not be discussed in detail here due to their lesser relevance to the proposed

indication. One was the NEWEST trial, a randomized, phase 2 open-label trial comparing 16 weeks of neoadjuvant fulvestrant 500 mg IM monthly + 500 mg IM loading dose on day #14 versus fulvestrant 250 mg IM monthly in postmenopausal women (N=211) with newly diagnosed, operable, ER+ invasive breast cancer. The primary endpoint of the trial was Ki67 index in the tumor specimen after 4 weeks of treatment, and a key secondary endpoint was Ki67 after 16 weeks of neoadjuvant treatment. At week 4, there was significantly greater reduction in Ki67 in the higher dose arm (mean % change: -79% versus -48%, p<0.0001). At week 16, the difference in Ki67 between the two arms had diminished in magnitude (-77% versus -63%).

The other was the FIRST trial, a randomized, open-label trial comparing fulvestrant 500 mg IM monthly + 500 mg IM loading dose to anastrozole 1 mg PO daily in postmenopausal women (N=205) with advanced breast cancer and either no prior endocrine therapy for advanced breast cancer or endocrine therapy for early-stage breast cancer completed at least 12 months prior to randomization. The primary endpoint was clinical benefit rate [(CBR), defined as complete response, partial response, or stable disease $\geq$ 24 weeks, as defined by modified RECIST criteria]. There was no significant difference between the treatment arms. The CBR was 73% in the fulvestrant arm compared with 67% in the anastrozole arm [OR 1.3; 95% CI 0.7-2.4; p-value=0.3].

The safety data from these trials were pertinent to this review and are discussed in the pooled safety analyses. The efficacy data from these trials were not reviewed in detail because the enrolled patient populations differed from the population with a labeled indication (e.g. the NEWEST trial enrolled newly diagnosed patients being treated in the neoadjuvant setting, and the FIRST trial enrolled women with no prior endocrine therapy for advanced breast cancer) and/or the study's endpoint was unacceptable for regulatory purposes (e.g. change in Ki67 in the NEWEST trial).

6 Review of Efficacy

Efficacy Summary

The phase 3 trial supporting this supplemental NDA was the CONFIRM trial. This was a randomized, international, double-blind, parallel-group, active control study that enrolled 736 postmenopausal women with advanced estrogen receptor-positive breast cancer who had relapsed while on adjuvant endocrine therapy or progressed on endocrine therapy for advanced breast cancer. Patients were eligible with either measurable disease or bone metastases in the absence of measurable disease. Patients with "life-threatening visceral involvement" were excluded from participation. Subjects were randomly assigned in a 1:1 allocation to receive either fulvestrant 250 mg IM every 4 weeks + placebo injection (control arm) or fulvestrant 500 mg IM every 4 weeks with an additional 500 mg dose on day #14 the first month (investigational arm).

Treatment was to continue until disease progression or unacceptable treatment-related toxicity.

The primary endpoint of the study was progression-free survival [(PFS), defined as the interval between the date of randomization and the date of disease progression or death, whichever occurred first]. Key secondary endpoints included overall survival [(OS), the interval between the date of randomization and subject's death from any cause], and response rate [(RR), the proportion of subjects in the evaluable population, defined as all randomized subjects with measurable disease at baseline who received at least one dose of study drug, had at least one post-baseline tumor assessment, and achieved a complete or partial response by RECIST criteria].

Baseline radiographic assessments were to have been performed within 4 weeks of starting study treatment. Radiographic assessments were then to be performed every 12 +/- 2 weeks until disease progression. Follow-up for survival was to occur every 12 weeks. First subsequent therapy after discontinuing study treatment was to be documented. Assessment of PFS was handled differently in patients with and without measurable disease at baseline and is discussed in further detail in Section 6.1.4.

In the fulvestrant 500 mg arm, 5% of subjects either had no baseline RECIST assessment or a baseline assessment outside of the required 4 week window compared with 10.2% in the fulvestrant 250 mg arm. As eligibility criteria permitted, approximately one-third of study subjects did not have measurable disease at baseline. These subjects had either only bone metastases (20%) or bone metastases with additional non-measurable disease outside the bone (10%). For these subjects, disease progression was defined as one or more new lytic bone lesions, a new lesion outside the bone, or unequivocal progression of existing bone lesions. Patients with progression detected by bone scan were to have confirmation with an additional imaging modality.

Based upon the FDA analysis of the primary endpoint, there was a statistically significant improvement in the primary endpoint of PFS (HR 0.80, 95% CI 0.68, 0.94), $p < 0.006$ favoring the fulvestrant 500 mg arm. This corresponded to a 1.1 month improvement in median PFS. Supportive of the primary endpoint was a trend for an improvement in OS (HR 0.84, 95% CI 0.69, 1.03), p=0.09 unadjusted for multiplicity, also favoring the fulvestrant 500 mg arm. This corresponded to a 2.3 month improvement in median OS. Both PFS and OS data were mature at the time of the sNDA submission.

6.1 Indication

The Sponsor's current labeled indication is:

Faslodex is indicated for treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

The current sNDA submission proposes a change in dose and schedule from the currently approved 250 mg IM every 28 days to 500 mg IM every 28 days with an additional 500 mg IM dose on day #14 of the first month of treatment.

6.1.1 Methods

Study Title: "A Randomised, Double-Blind, Parallel-group, Multicentre, Phase III Study Comparing the Efficacy and Tolerability of Fulvestrant (FASLODEX™) 500 mg with Fulvestrant (FASLODEX™) 250 mg in Postmenopausal Women with Oestrogen Receptor Positive Advanced Breast Cancer Progressing or Relapsing after Previous Endocrine Therapy"

Protocol No. D6997C00002

6.1.1.1 Study Objectives:

1) To compare the efficacy of fulvestrant 500 mg treatment with fulvestrant 250 mg treatment in terms of time to progression

2) To compare objective response rate, overall survival, other efficacy endpoints, and safety of fulvestrant 500 mg treatment with fulvestrant 250 mg treatment

Table 4: Landmark Events in the CONFIRM Trial

Event	Date
First subject randomized	02/08/2005
Last subject randomized	08/31/2007
Data cut-off for original sNDA submission	02/28/2009
Data cut-off for Safety Update	10/30/2009
Submission of sNDA	11/13/2009
Submission of Safety Update	03/10/2010

6.1.1.2 Study Endpoints:

Primary Endpoint:

The primary endpoint was PFS, defined as the interval between the date of randomization and the date of disease progression or death due to any cause, whichever occurred first. Subjects who remained on study without documented disease progression or death at the time of data cutoff for analysis were to be censored for PFS on the date of the last evaluable disease assessment.

Reviewer Note: The primary endpoint of the CONFIRM trial was progression-free survival (PFS), defined as time from randomization to disease progression or death due to any cause. This was referred to as time to progression (TTP) by the Sponsor in both the Sponsor's protocol and the sNDA submission, but will be referred to as PFS by convention for the purposes of this review and for product labeling.

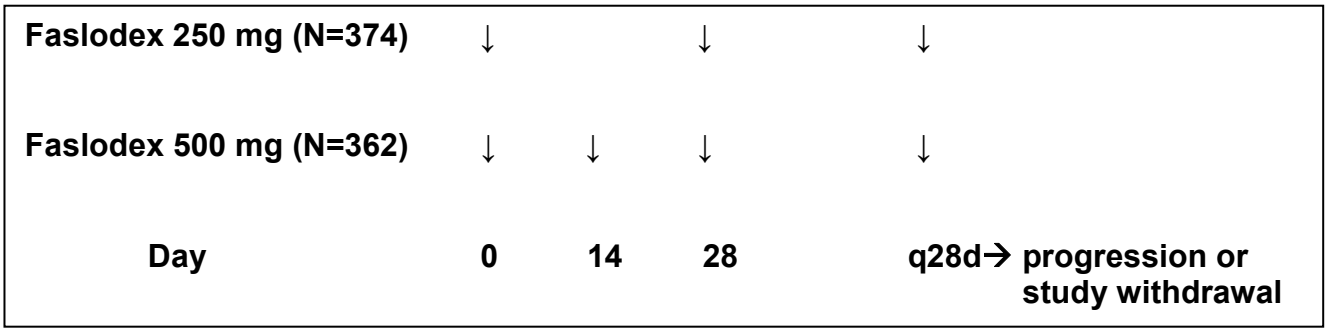
Secondary Endpoints:

Key secondary efficacy endpoints were OS (the interval between the date of randomization and the subject's date of death from any cause) and RR (the proportion of subjects in the evaluable population, defined as all randomized subjects who received at least one dose of study drug and who had at least one post-baseline tumor assessment, who achieved a complete or partial response by RECIST criteria).

6.1.1.3 Study Design

The CONFIRM trial was a randomized, international, double-blind, placebo-controlled trial. Postmenopausal women with ER+ advanced breast cancer who had relapsed while on or within 12 months of completing adjuvant endocrine therapy or who had progressed while on first endocrine therapy for advanced disease were eligible.

Figure 6: Treatment Dose and Schedule in the CONFIRM Trial



A total of 736 subjects were randomly assigned in a 1:1 allocation to the two treatment arms:

- Faslodex 500 mg IM on day 0, day 14, day 28, and every 28 days thereafter
- Faslodex 250 mg IM on day 0, day 28, and every 28 days thereafter

Treatment was to continue until disease progression or unacceptable treatment-related toxicity.

Baseline imaging was to be performed within 4 weeks prior to initiating study drug. Disease assessments were to be performed every 12 +/- 2 weeks until documented disease progression. Patients with bone metastases at baseline were also to have bone scans or skeletal surveys every 12 +/- 2 weeks. Imaging studies were to be performed using the same imaging modality. Contact for survival data was to occur at least every 12 weeks until death or the final survival analysis endpoint had been met, whichever occurred first.

Table 5: CONFIRM Study Calendar

Study Plan	Screening Phase	Treatment Phase									Treatment Disc.[j]	Survival Phase[j]
Visit	Screening[a]	1[b]	2 (Day 14)	3	4	5	6	7	8	9[c] onwards (every 12 weeks until progression)		
Week(s)	-3 to 0	0	2 (Day 14)	4	8	12	16	20	24	36 and onwards		
Informed consent	X											
Medical history	X											
Demography	X											
Inclusion/exclusion criteria	X											
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X[d,j]	
ECG[e]	X[e]											
Physical examination (including WHO performance status)	X	X		X	X	X	X	X	X	X	X	
Vital Signs (blood pressure, heart rate)		X		X	X	X	X	X	X	X	X	
Weight and height[p]		X[p]		X	X	X	X	X	X	X	X	
Haematology/clinical chemistry[f]	X	X		X		X			X	X	X	
Chest X-ray or CT scan of the chest	X[g]											
Bone scan or skeletal survey	X[k]					X[l]			X[l]	X[l]	X[l]	
Tumour assessment[e]	X[g]					X			X	X	X	
Randomised treatment		X	X	X	X	X	X	X	X[i]	X[i]		
AEs	X	X	X	X	X	X	X	X	X	X	X[d]	
Survival contact												X[h,j]
Informed consent for tissue biomarker research	X											
Optional tumour tissue samples for biomarker analysis (if available)[m]		X										
FACT-B HRQoL Questionnaire[n]		X		X	X	X	X	X	X		X[o]	

[a] Within 3 weeks before randomisation.
[b] Visit 1/Day 0 was to occur no more than 1 week after randomisation and no more than 4 weeks after tumour assessment.

[c] Assessment by RECIST every 12 (±2) weeks from Visit 1 until progression. Tumours were followed using same methodology at each assessment. For patients with an objective response (OR) of complete response (CR) or partial response (PR), confirmation of response by repeat imaging had to be performed at 4 weeks (or as soon as possible thereafter) following the date of response.
[d] Adverse event (AE) and concomitant therapy follow-up for 8 weeks after last injection.
[e] An ECG assessment had to be recorded within 3 weeks prior to randomisation and repeated if any cardiac AEs occurred.
[f] Laboratory assessments (haematology and clinical chemistry) were performed before randomisation, before treatment (unless treatment was given within 7 days following screening assessments), at Weeks 4 and 12, and every 12 weeks thereafter, until withdrawal from randomised treatment.
[g] Within the 4 weeks before treatment.
[h] Contact for survival after progression every 12 weeks until death or until the final survival analysis endpoint had been met, whichever occurred first.
[i] Treatment continued to be given every 28 (±3) days
[j] First subsequent systemic breast cancer therapy received following discontinuation of randomised treatment and details of response to treatment were collected.
[k] Patients must have had a bone scan within 8 weeks before treatment or a skeletal survey within 4 weeks before treatment. Any hotspots identified on the bone scan had to be confirmed by X-ray, computed tomography (CT) scan or magnetic resonance imaging (MRI), within 4 weeks prior to treatment.
[l] All patients with metastatic bone lesions at baseline, had to have bone scans or skeletal surveys every 12 weeks (±2 weeks) until progression. Additional bone scans or skeletal surveys were performed if clinically indicated. Abnormalities found on subsequent bone scans must have also been confirmed by X-ray, CT scan, or MRI.
[m] A tumour block (paraffin-embedded tumour tissue), if available, from either the primary tumour or a metastatic site was to be sent to the central laboratory in those patients who gave separate consent.
[n] HRQoL data were collected at baseline and at every 4 weeks for the first 24 weeks. HRQoL data were collected in selected countries/centres, for 145 patients.
[o] A HRQoL questionnaire also had to be completed at the treatment discontinuation visit if this occurred before 24 weeks.
[p] Height was only captured at Visit 1.
ECG:Electrocardiogram; CT:Computed tomography, FACT-B HRQoL:Functional Assessment of Cancer Therapy-Breast cancer – health-related quality of life; Treatment discon.:Treatment discontinuation.

6.1.1.4 Study Eligibility Criteria

Postmenopausal women with advanced or metastatic ER+ breast cancer who had relapsed during or within 12 months of completion of adjuvant endocrine therapy, or who had progressed on endocrine therapy for advanced breast cancer were eligible. Patients were permitted to have received adjuvant chemotherapy and no more than one prior regimen of chemotherapy and/or endocrine therapy for advanced disease. Patients with life-threatening visceral metastases were excluded. Of note, patients were not required to have measurable disease; patients with metastatic disease limited to the bones with or without additional sites of disease were also eligible. Chronic bisphosphonate therapy was not permitted.

Complete study eligibility criteria are shown below.

Inclusion Criteria

- Provision of written informed consent
- Histological/cytological confirmation of breast cancer
- Documented ER+ status of primary or metastatic tumor tissue, according to the local laboratory parameters
- Requiring endocrine therapy:
    - Relapsing during, or within 12 months of completion of, adjuvant endocrine therapy (tamoxifen, toremifene or AIs such as anastrozole, letrozole and exemestane), or
    - Progressing on an endocrine therapy (tamoxifen, toremifene or AIs such as anastrozole, letrozole and exemestane) provided that this endocrine treatment was started at least 12 months after the completion of adjuvant endocrine treatment, or

    - Progressing on an endocrine therapy (tamoxifen, toremifene or AIs such as anastrozole, letrozole and exemestane) given as first treatment for patients with de novo advanced breast cancer
- Fulfilling one of the following criteria:
    - Patients with measurable disease as per RECIST criteria. This is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$ 20 mm with conventional techniques or as $\geq$ 10 mm with spiral CT scan.
    - Patients with bone lesions, lytic or mixed (lytic and sclerotic), in the absence of measurable disease as defined by RECIST.
- Postmenopausal woman, defined as a woman fulfilling any 1 of the following criteria:
    - Age $\geq$ 60 years
    - Age ≥ 45 years with amenorrhea ≥ 12 months with an intact uterus
    - Having undergone a bilateral oophorectomy
    - Follicle stimulating hormone (FSH) and estradiol levels in postmenopausal range (utilizing ranges from the local laboratory facility)
    - In patients who had previously been treated with a luteinizing hormone releasing hormone (LHRH) analog, the last dose must have been administered more than 4 months prior to randomization, menses must not have restarted, and FSH and estradiol levels must also have been in the postmenopausal range (utilizing ranges from the local laboratory facility).
- WHO performance status 0, 1 or 2.

<u>Exclusion Criteria</u>

- Presence of life-threatening metastatic visceral disease, defined as extensive hepatic involvement, or any degree of brain or leptomeningeal involvement (past or present), or symptomatic pulmonary lymphangitic spread. Patients with discrete pulmonary parenchymal metastases were eligible, provided their respiratory function was not compromised as a result of disease.
- More than one regimen of chemotherapy for advanced disease (patients previously treated with one regimen of chemotherapy for advanced disease were allowed as long as their immediate past treatment was an anti-estrogen or aromatase inhibitor).
- More than one regimen of endocrine therapy for advanced disease (oophorectomy, ovarian ablation, or LHRH analog therapy did not count as endocrine therapies in this context)
- Extensive radiation therapy within the last 4 weeks (greater than or equal to 30% marrow or whole pelvis or spine) or cytotoxic treatment within the past 4 weeks prior to screening laboratory assessment, or strontium-90 (or other radiopharmaceuticals) within the past 3 months.

- Treatment with a non-approved or experimental drug within 4 weeks before randomization.
- Current or prior malignancy within previous 3 years (other than breast cancer or adequately treated basal cell or squamous cell carcinoma of the skin or in-situ carcinoma of the cervix).
- Any of the following laboratory values:
    - Platelets <100 × 109/L
    - Total bilirubin >1.5 × upper limit reference range (ULRR)
    - ALT or AST >2.5 × ULRR if no demonstrable liver metastases or >5×ULRR in presence of liver metastases.
- Bleeding diathesis (i.e. disseminated intravascular coagulation, clotting factor deficiency), or long-term anticoagulant therapy (other than anti-platelet therapy and low dose warfarin)
- History of hypersensitivity to active or inactive excipients of fulvestrant and/or castor oil.
- Any severe concomitant condition which made it undesirable for the patient to participate in the trial or which would jeopardize compliance with the CSP, e.g. uncontrolled cardiac disease or uncontrolled diabetes mellitus.

6.1.1.5 Study Enrollment

A total of 736 patients were randomized to participate in the CONFIRM trial at 128 sites in 17 countries. The trial was conducted in both the United States and several countries abroad. The United States contributed 4.2% of the overall study population. The first patient was randomized on 02/08/2005, and the last patient was randomized on 08/31/2007. The data cutoff for the primary analysis submitted in the sNDA was 02/28/2009, at which time 618 progression events had been observed.

6.1.1.6 Statistical Analysis Plan

Approximately 720 patients were to be randomized to observe 632 events (progression or death). For the primary endpoint of PFS, the primary analysis was an unadjusted log-rank test carried out in the intent-to-treat (ITT) population. The treatment effect was to be estimated using the hazard ratio of fulvestrant 500 mg to fulvestrant 250 mg together with the corresponding 95% confidence interval (CI) and p-value. Superiority was to be declared if the 2-sided p-value for the treatment comparison was ≤ 0.05. The secondary analysis was a Cox proportional hazard model with treatment factor and baseline prognostic covariates. A formal analysis of OS using an unadjusted log-rank test in the ITT population was planned for when ≥ 50% of patients had died.

6.1.2 Demographics

Patient demographics and tumor characteristics were generally well-balanced between arms in the CONFIRM trial. All patients were postmenopausal women. The mean age was 61 yrs in both arms [range: 23-91]. Approximately 60% of subjects were < 65 years old. More than 96% of subjects were Caucasian. Two-thirds of subjects' tumors were both ER+ and PR+. Although nearly all subjects had distant metastatic disease (98%), only 70% of subjects had measurable disease at baseline, and approximately 20% of subjects had metastatic disease limited to bone. There were slightly fewer patients in the fulvestrant 500 mg arm with measurable disease at baseline (66% versus 70%).

6.1.3 Subject Disposition

A total of 736 patients were randomized to the CONFIRM trial from 128 sites in 17 countries. In total, 663 patients (90%) had discontinued study treatment by the time of the data cut-off date. Discontinuations were more common in the fulvestrant 250 mg arm (N=343, 92%) than in the fulvestrant 500 mg arm (N=320, 89%). The most common reason for treatment discontinuation in both arms was disease progression (N=258 in fulvestrant 500 mg arm; N=278 in fulvestrant 250 mg arm). Other reasons for discontinuation of study treatment shown as the fulvestrant 500 mg arm versus the fulvestrant 250 mg arm included: death (8 versus 13), adverse event (8 versus 6), not willing to continue treatment (5 versus 5), not willing to continue study (13 versus 11), eligibility criteria not met (3 versus 4), lost to follow-up (3 versus 1), protocol non-compliance (2 versus 2), and other (20 versus 23), which included disease progression determined by non-RECIST criteria, initiation of prohibited treatment such as radiotherapy, and patient moving out of area. At the time of the original data cut-off for the sNDA submission, there were 41 patients still being treated on the fulvestrant 500 mg arm and 31 patients on the fulvestrant 250 mg arm.

All patients randomized were included in the ITT population. There were 48 patients on the fulvestrant 500 mg arm and 58 patients on the fulvestrant 250 mg arm with important protocol deviations. Comparing the fulvestrant 500 mg arm to the fulvestrant 250 mg arm, these included failure to meet eligibility criteria (7.2% versus 7.8%), screening RECIST assessments not done within specified time window (4.4% versus 7.0%), screening RECIST assessments not done at all (0.6% versus 3.2%), and others.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint of the CONFIRM trial was progression-free survival (PFS), defined as time from randomization to disease progression or death due to any cause.

Patients were not required to have measurable disease to enroll in the CONFIRM trial. PFS was assessed differently for patients with (N=501) and without measurable disease (N=225) at baseline.

For patients with measurable disease at baseline, up to 10 measurable target lesions (≤ 5 per organ) were selected at screening, measured at the time of objective tumor assessment every 12 +/- 2 weeks, and reported according to RECIST criteria. All non-target lesions were also to be monitored during the study, and non-target lesions was to be recorded at the time of each radiographic assessment as present, present with progression, or absent. Patients with progression of target lesions (according to classic RECIST criteria), clear progression of existing non-target lesions, or appearance of one or more new lesions were deemed to have progressed. Missing target lesion data were handled as follows. If all target lesion measurements were missing, the overall visit response was classified as not evaluable unless there was progression of non-target lesions or new lesions. If measurements for more than one-third of target lesions recorded at baseline were missing, the response was classified as not evaluable unless the sum of longest diameters (LDs) of non-missing target lesions met RECIST criteria for PD. If less than one-third of target lesions recorded at baseline were missing, the results were "scaled up" based on baseline sizes to give an estimated sum of LDs, which was then used in calculations.

For patients with only bone metastases at baseline (i.e. no target lesions and therefore no measurable disease at baseline), patients were to be imaged every 12 +/- 2 weeks, including bone scan or skeletal survey and could only be classified into one of three categories: not evaluable, stable disease, or progressive disease. Progressive disease was defined as "appearance of one or more new lytic bone lesions, appearance of one or more new lesions outside of bone, or unequivocal progression of existing bone lesions".

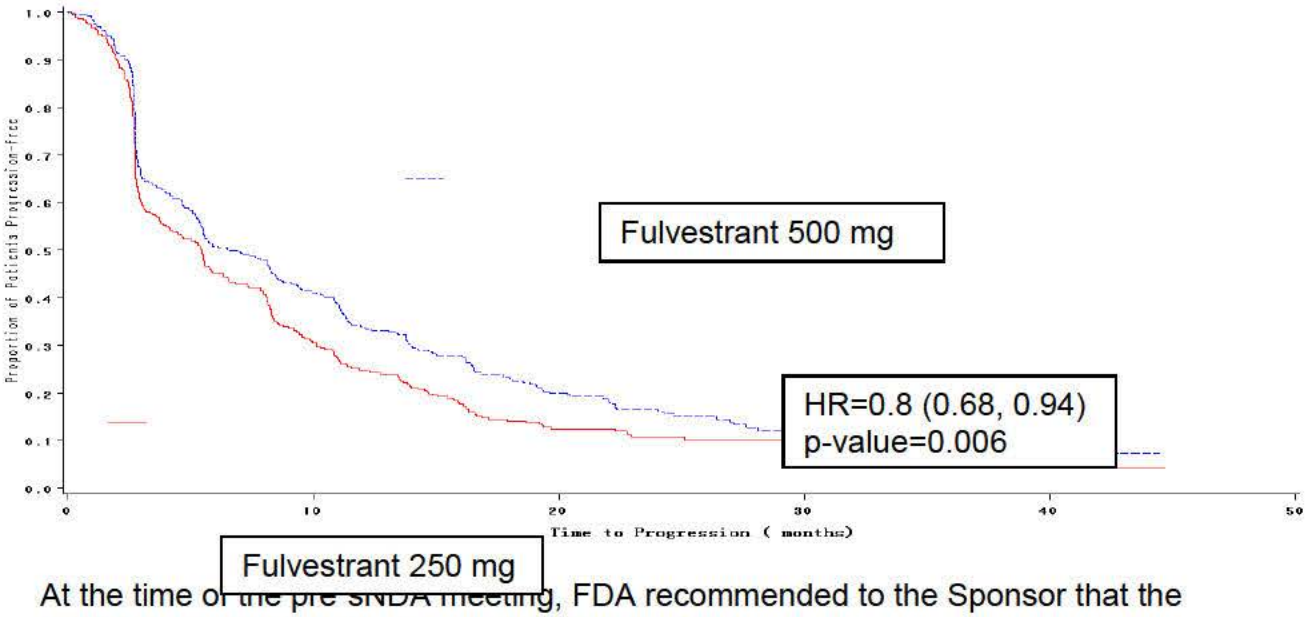
For patients who progressed, PFS was defined as date of earliest evidence of disease progression or death from any cause minus date of randomization. Patients who were not known to have progressed or died at the time of the data cut-off, including those who were lost to follow-up, had PFS censored at the date of the last evaluable disease assessment per RECIST.

The analysis of PFS was planned to take place when 632 PFS events had been observed but was performed when 618 events had been observed. The OS analysis was to be undertaken when >50% of the total number of PFS events had been observed. A total of 378 deaths had been observed by the time of the sNDA submission, and therefore the survival data are mature.

Reviewer Note: The FDA analysis of the primary endpoint of PFS demonstrated a statistically significant 20% reduction in the risk of progression or death, which corresponded to a 1.1 month improvement in median PFS, favoring the fulvestrant 500 mg arm. Note that although the PFS curves separate from approximately 3 months to 30 months of follow-up, the curves briefly converge at the observed median PFS. This raises the possibility that the difference in median PFS of 1.1 months is an underestimation of the difference in treatment effect between the two arms. Supportive of the primary endpoint was a trend demonstrating a 16% reduction in the risk of death, corresponding to a 2.3 month improvement in median OS, also favoring the fulvestrant 500 mg arm. Survival data were mature at the time of the sNDA submission.

The Kaplan-Meier curve for PFS by FDA analysis is shown in Figure 7. The hazard ratio of 0.80 (95% CI 0.68, 0.94) favored the fulvestrant 500 mg arm and was statistically significant. This corresponded to an approximately one month prolongation of PFS (median PFS 6.5 months versus 5.4 months) for patients receiving the higher dose.

Figure 7: Kaplan-Meier Curve of PFS, CONFIRM Trial, ITT Population (FDA Analysis)



At the time of the pre sNDA meeting, FDA recommended to the Sponsor that the following censoring rules be used for the analysis:

"PFS data should be censored on the date of the last tumor assessment documenting absence of progression for patients:

- Who were alive, on study and progression-free at the time of the analysis

- Who were given/changed therapy other than the study treatment prior to observing progression
- Who discontinued (due to personal preference or toxicity)/ withdrew or were lost to follow-up
- For whom documentation of disease progression or death occurred after ≥ 2 consecutive missed tumor assessments."

According to these censoring rules, a total of 142 patients (19.2%) were censored for PFS in the FDA analysis. Censoring occurred slightly more commonly in the fulvestrant 500 mg arm (N=77, 21.3%) than in the fulvestrant 250 mg arm (N=65, 17.4%). A total of 594 events had occurred at the time of the original data cut-off, of which 285 (78.7%) were in the fulvestrant 500 mg arm and 309 (82.6%) were in the 250 mg arm. The majority of these events were disease progression (91.7%), which represented 91.2% of events on the 500 mg arm and 92.2% of events on the 250 mg arm. The events recorded also included 49 deaths, of which 25 were on the 500 mg arm and 24 on the 250 mg arm. These results are shown in Table 6 below.

Table 6: PFS Results, CONFIRM Trial, ITT Population (FDA Biostatistics Analysis)

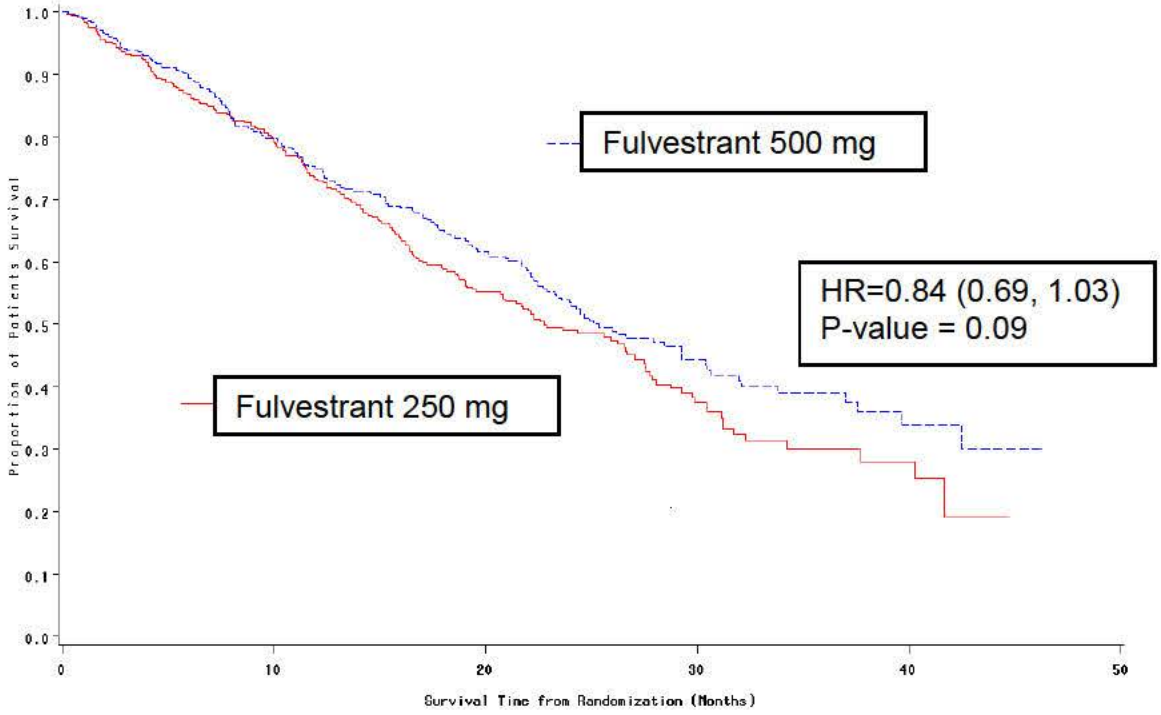
	Fulvestrant 500 mg (N=362)	**Fulvestrant 250 mg (N=374)**
Patients Censored (%)	77 (21.3)	65 (17.4)
Events (%)	285 (78.7)	309 (82.6)
Death (%)	25 (8.8)	24 (7.8)
PD (%)	260 (91.2)	285 (92.2)
Median PFS, mos (95% CI)	6.5 (5.5, 8.3)	5.4 (4.0, 5.9)
Hazard ratio (95% CI)	0.80 (0.68, 0.94)	
Log-rank p-value	0.006	

6.1.5 Analysis of Secondary Endpoints(s)

Secondary efficacy endpoints that will be considered in further detail include overall survival and objective response rate.

The hazard ratio for OS was 0.84 (95% CI 0.69, 1.03; p=0.09, unadjusted for multiplicity) favoring the fulvestrant 500 mg arm. This corresponded to a 2.3 month improvement in median OS for the 500 mg arm. The Kaplan-Meier curve for OS is shown in Figure 8 below.

Figure 8: Overall Survival Kaplan-Meier Curve, CONFIRM Trial, ITT Population (FDA Analysis)



There had been 378 deaths observed at the time of the sNDA submission, of which 175 (48.3%) were in the fulvestrant 500 mg arm and 203 (54.3%) were in the 250 mg arm. The median OS in months was 25.1 months (95% CI 22.9, 30.4) in the 500 mg arm and 22.8 months (95% CI 19.5, 27.5) in the 250 mg arm. There were 358 patients censored for OS, of whom 187 (51.7%) were in the fulvestrant 500 mg arm and 171 (45.7%) were in the 250 mg arm. These results are shown in Table 7 below.

Table 7: Overall Survival, CONFIRM Trial, ITT Population (FDA Biostatistics Analysis)

	Fulvestrant 500 mg (N=362)	**Fulvestrant 250 mg (N=374)**
Number Censored (%)	187 (51.7)	171 (45.7)
Number of Deaths (%)	175 (48.3)	203 (54.3)
Median OS, mos (95% CI)	25.1 (22.9, 30.4)	22.8 (19.5, 27.5)
Hazard Ratio (95% CI)	0.84 (0.69, 1.03)	

	Fulvestrant 500 mg (N=362)	Fulvestrant 250 mg (N=374)
Log-rank p-value	0.09	

The overall response rate, assessed only in the subset of the population with measurable disease present at study entry, was similar in the two arms. These data are shown in Table 8 below. There were 68 investigator-assessed responses recorded, 33 (13.8%) in the fulvestrant 500 mg arm and 38 (14.6%) in the 250 mg arm. Of these, 66 out of 71 (93%) were partial responses. There were 5 subjects with complete responses, of whom 4 were in the fulvestrant 500 mg arm.

Table 8: Summary of Best Objective Response per RECIST, Evaluable Population, CONFIRM Trial

Best Objective Response	Number (%) of subjects	
	Fulvestrant 500 mg (N=240) N (%)	Fulvestrant 250 mg (N=261) N (%)
Overall Objective Response	33 (13.8)	38 (14.6)
Complete Response	4 (1.7)	1 (0.4)
Partial Response	29 (12.1)	37 (14.2)
Stable Disease	98 (40.8)	103 (39.5)
Progressive Disease	102 (42.5)	117 (44.8)
Not Evaluable†	7 (2.9)	3 (1.1)

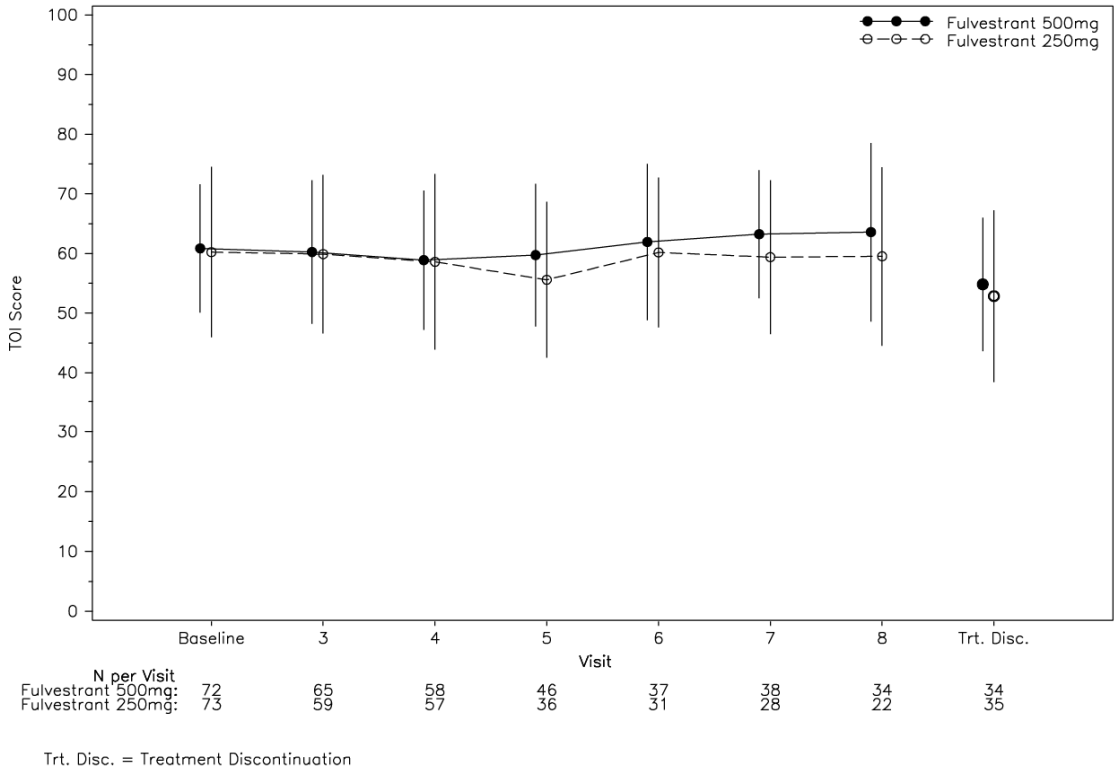
†Subjects in this category had no evaluable follow-up assessments post-randomization.

6.1.6 Other Endpoints

Health related quality of life (HRQoL) was assessed in a subset of patients (N=145) enrolled in the CONFIRM trial using the FACT-B trial outcome index (TOI).

A baseline FACT-B TOI questionnaire was completed by 145 (82%) of 176 patients randomized in the countries that participated in evaluation of HRQoL. HRQoL remained relatively high over the course of the study with a mean TOI score of approximately 60 out of 92. The Sponsor's plot of TOI by treatment time point, shown in Figure 9, shows no significant difference between the two arms.

Figure 9: FACT-B TOI: CONFIRM Trial, Full Analysis Set (Sponsor's Figure)



The Sponsor's linear mixed model analysis of TOI similarly demonstrated no significant difference between the two arms (estimated difference=0.91 [95% CI -0.33 to 2.15]; p=0.15). These data are shown in Table 9 below.

Table 9: FACT-B TOI: CONFIRM Trial, Full Analysis Set (Sponsor's Table)

Longitudinal analysis model adjusted for baseline covariates	Estimated difference in TOI	Lower 95% CI	Upper 95% CI	p-value
Fulvestrant 500 mg vs Fulvestrant 250 mg	0.91	−0.33	2.15	0.1485

A difference >0 favours fulvestrant 500 mg whereas a difference of <0 favours fulvestrant 250 mg.

In summary, there was no significant difference in the FACT-B Trial Outcome Index between treatment arms among the subset of study subjects enrolled in countries chosen to participate in the HRQoL assessment.

6.1.7 Subpopulations

All patients enrolled in the CONFIRM trial were postmenopausal women. Women ≥ 65 years old, who more often have strongly hormone receptor positive tumors and a relatively indolent course of metastatic breast cancer, had longer PFS than women < 65 years old, regardless of assigned treatment arm. The hazard ratio for PFS comparing the two treatment arms was similar for the two age groups [HR 0.77 (0.63, 0.95) for women < 65 years old versus HR 0.85 (0.65, 1.10) for women ≥65 years old].

The population of the CONFIRM trial was > 96% Caucasian, and therefore, it is not possible to comment on the interaction of ethnicity and dose responsiveness to fulvestrant. See also Section 4.4.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

This is addressed throughout the review as this supplement is to evaluate the safety and efficacy of a change in dose of an approved drug.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable

6.1.10 Additional Efficacy Issues/Analyses

An unplanned subgroup analysis of patients having disease limited to bone at baseline versus those with measurable disease demonstrates a significant difference in median PFS between the two groups. The effect of increasing the dose of fulvestrant for the patients with baseline measurable disease (N=426) is minimal and results in an improvement in median PFS of 0.3 months (HR 0.84). For patients without baseline measurable disease (N=192), the improvement in median PFS is 2.9 months (HR 0.74). Similarly, in subjects without baseline visceral involvement (N=202), the improvement in median PFS is 4.6 months (HR 0.74) whereas subjects with baseline visceral involvement (N=416) had an improvement in median PFS of only 1.1 month (HR 0.82). In the smaller FINDER 1 and FINDER 2 trials, which enrolled only subjects with measurable disease (i.e. not bone-confined) and contained two arms identical in treatment dose/schedule to those in the CONFIRM trial, there was no significant difference in the primary endpoint of RR. This likely reflects relative endocrine resistance at baseline in the patients enrolled.

Reviewer Note: It is possible that the trial showed only a modest improvement in median PFS because of the heterogeneity of patients enrolled. Most patients with hormone receptor-positive breast cancer develop bone metastases as an isolated first site of recurrence. By the time that visceral metastases develop, breast cancers are often relatively endocrine-resistant despite their hormone receptor status. In such patients, increasing the dose of endocrine therapy has historically not been effective in overcoming endocrine resistance. One would predict that inclusion of such patients would dilute the apparent treatment effect for the overall study population.

Although there are significant challenges to accurate assessment of PFS in patients with metastatic cancer limited to the bones, many of these could be minimized with a carefully selected definition of progression and a randomized, double-blind design in a relatively homogeneous population of patients with metastatic hormone receptor-positive breast cancer limited to the bones. This is an example of a trial that could be greatly improved with an enrichment strategy, i.e. enrolling only patients likely to be sensitive to the proposed intervention of high-dose fulvestrant, namely those with isolated bone metastases.

7 Review of Safety

Safety Summary

The primary trial supporting the safety of fulvestrant in this supplemental NDA was the CONFIRM trial. As described in the Efficacy Summary, this was a randomized, international, double-blind, parallel-group, active control study that enrolled 736 postmenopausal women with advanced estrogen receptor-positive breast cancer who had relapsed while on adjuvant endocrine therapy or progressed on endocrine therapy for advanced breast cancer. Subjects were randomly assigned in a 1:1 allocation to receive either fulvestrant 250 mg IM every 4 weeks + placebo injection (control arm) or fulvestrant 500 mg IM every 4 weeks with an additional 500 mg dose on day #14 the first month (investigational arm). Treatment was to continue until disease progression or unacceptable treatment-related toxicity. Physical examination and vital signs were performed at baseline and every 4 weeks until week 24, then every 12 weeks until study withdrawal. Laboratory assessments including complete blood counts and chemistry panels were performed at baseline, week 4, week 12, and every 12 weeks thereafter until study discontinuation. Patients were screened for adverse events at each visit.

There were 735 patients who received a first dose of fulvestrant in the CONFIRM trial and constitute the primary safety population analyzed in this sNDA. Of these, 361 were treated on the fulvestrant 500 mg arm. Pooled safety data using the CONFIRM, NEWEST, FINDER 1, and FINDER 2 trials, all of which included arms comparing

fulvestrant 500 mg to fulvestrant 250 mg monthly, were also examined for certain key safety outcomes. The pooled safety population included 1,127 subjects, of whom 567 were fulvestrant 500 mg.

There were fewer deaths observed overall in the fulvestrant 500 mg arm (N=174, 48.2%) than in the fulvestrant 250 mg arm (N=203, 54.3%). Of these deaths, 92% occurred more than 8 weeks after discontinuing study drug. Deaths while receiving fulvestrant, or within 8 weeks of discontinuation of treatment, were also less common on the fulvestrant 500 mg arm than the control arm (7.2% versus 8.8%).

Adverse events of grade $\geq$ 3 were infrequent in the CONFIRM trial, occurring in 15.4% of study participants overall. Grade $\geq$ 3 treatment-emergent AEs occurred in slightly fewer subjects in the fulvestrant 500 mg arm (N=53, 14.7%) than in the control arm (N=60, 16.0%). The most commonly reported grade $\geq$ 3 AEs were musculoskeletal disorders, gastrointestinal disorders, and injection site pain, which occurred in similar percentages of subjects in the two arms.

The percentage of patients who experienced at least one AE in the CONFIRM trial was slightly higher in the fulvestrant 500 mg arm (67.3%) than in the 250 mg arm (64.2%). Similar to the pattern observed for grade 3 adverse events, the most commonly reported classes of all-grade toxicities were musculoskeletal disorders, gastrointestinal disorders, and injection site pain without meaningful differences noted between the two arms. Of note, the CONFIRM trial included two injections (250 mg in each buttock for subjects on the investigational arm and 250 mg + a placebo for subjects on the control arm) for all subjects.

Reviewer Note: In routine clinical use, the incidence and/or severity of injection site pain is likely to be greater for patients receiving 500 mg monthly, who will require four intramuscular injections the first month then two injections monthly thereafter, than for patients receiving 250 mg, who will receive a single intramuscular injection monthly, without the addition of placebo injections as were used in the trial.

The pooled safety data from the CONFIRM, NEWEST, FINDER 1 and FINDER 2 trials (N=1127) demonstrated no clinically significant difference in the overall incidence of any grade AEs, grade $\geq$ 3 AEs, serious adverse events, deaths on study, or AEs leading to discontinuation of treatment in subjects treated with fulvestrant 500 mg monthly compared with those who received 250 mg monthly.

In summary, the adverse event profile of fulvestrant 500 mg monthly was similar to the known adverse event profile of fulvestrant 250 mg monthly, reflected in the current product labeling. The incidence of serious or fatal adverse events did not appear to be

significantly increased with the higher dose in either the CONFIRM trial or the pooled safety population.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary trial used to evaluate safety was the CONFIRM trial, described in detail in Section 6.1.1. Safety data from the two relevant arms of the FINDER1 and 2 trials, and safety data from the NEWEST trial, all described in Section 5.3, were also reviewed for evaluation of less common adverse events. Pooled data from the CONFIRM, NEWEST, FINDER 1, and FINDER 2 trials (which contained arms comparing fulvestrant 500 mg monthly with an additional 500 mg dose on day 14 to fulvestrant 250 mg monthly) were also used to compare the incidence of all grade toxicity, grade ≥ 3 toxicity, serious adverse events, adverse events leading to discontinuation, and deaths on study. These results are described in Section 7.1.3 and shown in Table 10.

7.1.2 Categorization of Adverse Events

Adverse events were coded using MedDRA and appear to have been appropriately converted from verbatim to preferred terms based upon a random audit of the AEVCC.xpt dataset of the CONFIRM trial.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The primary safety analysis of this sNDA was conducted in the safety population of the CONFIRM trial. Selected additional safety analyses were conducted using pooled safety data from the CONFIRM, NEWEST, FINDER 1 and FINDER 2 trials (N=1127), all of which included a fulvestrant 500 mg arm and a fulvestrant 250 mg arm. The pooled safety data demonstrated no clinically meaningful difference in the overall incidence of any grade AEs, grade ≥ 3 AEs, serious adverse events, deaths on study, or AEs leading to discontinuation of treatment in subjects treated with fulvestrant 500 mg monthly compared with those who received 250 mg monthly. These data are shown in Table 10 below.

Table 10: Important Safety Outcomes, Pooled Safety Population, (CONFIRM, NEWEST, FINDER 1, FINDER 2 Trials)

	Number (%) of Patients, by Treatment	
	Fulvestrant 500 mg (N=560) N (%)	Fulvestrant 250 mg (N=567) N (%)
Any AE	393 (70.2)	387 (68.3)
Grade ≥ 3 AE	84 (15)	83 (14.6)
Any SAE	48 (8.6)	43 (7.6)
Death on study	29 (5.2)	35 (6.2)
AE leading to discontinuation	11 (2.0)	13 (2.3)

7.2 Adequacy of Safety Assessments

The nature and frequency of safety assessments were appropriate based upon the well-characterized adverse event profile of fulvestrant when used at the currently approved dose of 250 mg IM monthly in a metastatic breast cancer population. The majority of adverse events that occur with fulvestrant are fall in the categories of injection site reactions, musculoskeletal pain, gastrointestinal symptoms, and vasomotor symptoms. Patients were screened for adverse events at each visit (i.e. every 4 weeks). Laboratory assessments including complete blood counts and chemistry panels were performed at baseline, week 4, week 12, and every 12 weeks thereafter until study discontinuation.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The extent and duration of drug exposure are consistent with the Office of Oncology Drug Products' standards for treatment of an advanced cancer population. Table 11 shows the mean and median durations of exposure to fulvestrant in the safety population of the CONFIRM trial.

Table 11: Duration of Exposure (CONFIRM Safety Analysis Set)

Duration	Fulvestrant 500 mg (N=361)	Fulvestrant 250 mg (N=374)
Mean (sd), months	10.3 (9.7)	8.2 (8.4)
Median (range), months	5.7 (0.3-47.3)	4.8 (0.2-45.6)

In addition to the 361 patients randomized to the fulvestrant 500 mg monthly + 500 mg day #14 dose in the CONFIRM trial, there were an additional 300 patients treated with

the same dose and schedule of fulvestrant in the NEWEST, FINDER1, FINDER 2, and FIRST trials. The mean duration of exposure across all five trials was 8.6 months.

Please refer to Section 6.1.2 for a discussion of the demographics of the study population of the CONFIRM trial. The subjects enrolled are broadly representative of the hormone receptor-positive postmenopausal population typically treated with fulvestrant in the metastatic breast cancer setting.

7.2.2 Explorations for Dose Response

This topic is covered throughout this review as the supplement is to address the safety and efficacy of a change in dose.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

In the CONFIRM trial, physical examination and vital signs were performed at baseline and every 4 weeks until week 24, then every 12 weeks until study withdrawal. Routine laboratory testing included chemistry panel and complete blood count performed at baseline, week 4, week 12, and every 12 weeks thereafter until study withdrawal. Adverse event information was collected every 4 weeks at the time of fulvestrant administration.

7.2.5 Metabolic, Clearance, and Interaction Workup

See Section 4.4.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Fulvestrant is the only marketed pure anti-estrogen. Based upon clinical experience with other drugs having a partial estrogen antagonist effect, such as the selective estrogen receptor modulators (e.g. tamoxifen), and other drugs that lower circulating estrogens, such as the aromatase inhibitors (e.g. anastrozole), the Sponsor pre-specified a number of adverse event categories to compare between the two arms, including gastrointestinal symptoms, musculoskeletal complaints, ischemic and thromboembolic events, vasomotor symptoms, and osteoporosis, among others. The results of this analysis, described in Section 7.3.5, did not demonstrate any significant difference between the dose levels other than a slightly increased incidence of vasomotor symptoms with the higher fulvestrant dose.

7.3 Major Safety Results

7.3.1 Deaths

At the time of the data cut-off for the original sNDA submission, 377 (51.3%) patients had died. For 359 of these patients (95.2%), the cause of death was listed as disease progression. There were fewer deaths observed overall in the fulvestrant 500 mg arm (N=174, 48.2%) than in the fulvestrant 250 mg arm (N=203, 54.3%). The majority (92%) of deaths reported as "on study" actually occurred more than 8 weeks after discontinuing fulvestrant. Deaths while on fulvestrant, or within 8 weeks of discontinuation of treatment, were slightly less common on the fulvestrant 500 mg arm than the control arm (7.2% versus 8.8%).

Reviewer Note: Fewer deaths were observed in the fulvestrant 500 mg arm, both on treatment and following discontinuation of study treatment. The majority of deaths were attributed to disease progression. Deaths due to adverse events were uncommon and observed in similar numbers on both study arms.

There were 11 patients reported in the CONFIRM trial to have experienced a fatal adverse event while on study. These patients were evenly divided between the fulvestrant 250 mg and 500 mg arms. These adverse events demonstrated no clear pattern or site of toxicity common to, or distinguishing between, the two dose levels. Only one patient, shown in italics, experienced an adverse event resulting in death (hypertension, in a patient on the control arm) that was deemed related to the study treatment according to the Investigator. The remaining AEs were judged to be "unrelated" by the Investigator.

Fatal adverse events reported in the CONFIRM Trial are outlined in Table 12 below.

Table 12: Fatal Adverse Events (CONFIRM Trial, Safety Population)

Patient ID	Age	Adverse Event	Time to AE onset (days)	Time to death (days)
Fulvestrant 500 mg				
E0140004	67	Intestinal adenocarcinoma	371	420
E0202002	58	Dyspnea	177	180
E0244009	81	Cardiopulmonary failure	14	14
E0251002	50	Abdominal pain	125	127
E0255006	43	Dyspnea	9	10

Patient ID	Age	Adverse Event	Time to AE onset (days)	Time to death (days)
Fulvestrant 250 mg (Control)				
E0154001	87	Acute myocardial infarction	55	55
E0180009	69	Completed suicide	19	19
E0236003	67	Meningitis	5	7
E0252005	61	Aspiration	23	23
E0256005	*63*	*Hypertension*	*48*	*51*
E0261026	66	Renal failure, acute	29	29

Subject E0256005, Fulvestrant 250 mg Arm (Cause of Death: Hypertension):
Subject E0256005 was a 63 year-old woman with a history of type II diabetes and advanced breast cancer for which she had undergone mastectomy on (b) (6). There was no reported past medical history of hypertension. She was randomized to the fulvestrant 250 mg arm of the CONFIRM trial, began study treatment on 03-13-2006, and received her first two doses of fulvestrant on 03-13-2006 and 04-10-2006. She presented with generalized weakness on study day #48, apparently prior to administration of fulvestrant, and was found to be hypertensive. No details have been provided as to the patient's hospital course, however the causality was assessed as related, and the patient died (b) (6) with cause of death listed as hypertension. No post-mortem evaluation was performed.

7.3.2 Nonfatal Serious Adverse Events

Adverse events of grade ≥ 3 were relatively uncommon in the CONFIRM trial, having been reported in only 15.4% of study participants. Grade ≥ 3 treatment-emergent AEs occurred in slightly fewer subjects in the fulvestrant 500 mg arm (N=53, 14.7%) than in the control arm (N=60, 16.0%) and were consistent with all-grade toxicities. These data are shown in Table 13 below.

Reviewer Note: Both all-grade and grade ≥ 3 AEs occurred in similar percentages of subjects in the two treatment arms. The most commonly reported classes of all-grade and serious AEs were musculoskeletal disorders, gastrointestinal disorders, and injection site pain.

The most commonly reported classes of grade ≥ 3 AEs were musculoskeletal disorders (4.1%), which occurred in 2.8% of subjects in the fulvestrant 500 mg arm and 5.3% of subjects in the control arm; gastrointestinal disorders (2.4%), which occurred in 3.6% of subjects in the fulvestrant 500 mg arm and 1.3% of subjects in the control arm; and general disorders/administration site conditions (2.3%), which occurred in approximately the same percentage in both arms.

Table 13: Grade ≥ 3 AEs Reported in ≥ 2 Subjects in Either Arm, CONFIRM Trial, Safety Population

Adverse Event	Fulvestrant 500 mg (N=361)		Fulvestrant 250 mg (N=374)	
	N	%	N	%
Overall†	**53**	**14.7**	**60**	**16**
Back pain	4	1.1	6	1.6
Vomiting	4	1.1	0	0
Arthralgia	3	0.8	2	0.5
Abdominal pain	3	0.8	1	0.3
AST increased	3	0.8	1	0.3
Ascites	3	0.8	0	0
Bone pain	2	0.6	5	1.3
Dyspnea	2	0.6	3	0.8
General physical health Deterioration	2	0.6	1	0.3
Diarrhea	2	0.6	0	0
Hypertension	2	0.6	1	0.3
Hyperglycemia	2	0.6	0	0
Hypokalemia	2	0.6	0	0
Neutropenia	2	0.6	0	0
Bronchitis	2	0.6	0	0
Asthenia	1	0.3	2	0.5
Musculoskeletal chest pain	1	0.3	2	0.5
Pain in extremity	0	0	4	1.1
Fatigue	0	0	4	1.1
Anxiety	0	0	3	0.8
Deep vein thrombosis	0	0	2	0.5
Syncope	0	0	2	0.5

†Note: Individual AE percentages do not add up to overall percentages because some patients experienced more than one grade ≥ 3 AE.

7.3.3 Dropouts and/or Discontinuations

At the time of the original data cut-off, 90.2% of subjects had discontinued study treatment. The majority of patients who discontinued study treatment (73%) did so due to objective disease progression. Discontinuations attributed to disease progression were more common in the fulvestrant 250 mg arm (N=278, 74.3%) than in the

fulvestrant 500 mg arm (N=258, 71.5%). Discontinuations due to adverse events were uncommon (N=14, 1.9%) and occurred in similar percentages of patients in the fulvestrant 250 mg (N=6, 1.6%) and the fulvestrant 500 mg (N=8, 2.2%) arms. Discontinuations due to "subject not willing to continue treatment" occurred in 5 patients in each arm, and those due to "subject not willing to continue study" occurred in 13 patients in the fulvestrant 500 mg arm and 11 patients in the control arm.

7.3.4 Significant Adverse Events

Refer to Section 7.3.5.

7.3.5 Submission Specific Primary Safety Concerns

The Sponsor identified several pre-specified categories of adverse events to compare between the arms based upon the mechanism of action and existing safety profile of fulvestrant and other anti-estrogens. These categories, which were comprised of several lower-level preferred terms, included: gastrointestinal disturbances, joint disorders, injection site reactions, hot flashes, urinary tract infection, ischemic cardiovascular disorders, thromboembolic events, vaginitis, weight gain, osteoporosis, and endometrial dysplasia. A comparison of these pre-specified adverse event categories is shown in Table 14 below.

This analysis demonstrated no meaningful difference between the two treatment arms. Although numbers of events were small, ischemic cardiovascular disorders and thromboembolic events were reported less frequently in the 500 mg arm than in the control arm.

Table 14: Submission-Specific Safety Concerns, Safety Population, CONFIRM Trial

AE Category	Fulvestrant 500 mg (N=361)		Fulvestrant 250 mg (N=374)	
	N	%	N	%
Gastrointestinal disturbances	73	20.2	76	20.3
Joint disorders	68	18.8	70	18.7
Injection site disorders	49	13.6	50	13.4
Hot flashes	30	8.3	23	6.1
Urinary tract infections	8	2.2	8	2.1
Ischemic cardiovascular disorders	5	1.4	7	1.9
Thromboembolic events	3	0.8	6	1.6
Vaginitis	3	0.8	1	0.3
Weight gain	1	0.3	1	0.3
Osteoporosis	1	0.3	0	0
Endometrial dysplasia	0	0	0	0

Based upon evidence from postmarketing surveillance that fulvestrant may result in increases in hepatic transaminases, an analysis for cases of severe hepatotoxicity in the safety population of the CONFIRM trial was undertaken. An analysis of individual function changes in liver function parameters comparing baseline to post-treatment values identified 22 subjects (13 in the fulvestrant 250 mg arm and 9 in the fulvestrant 500 mg arm) who experienced a post-baseline increase in AST, ALT, or bilirubin to CTC grade $\geq$ 3. These data are shown in Table 15 below.

Table 15: Number of Subjects with Changes in Liver Function Laboratory Values from Baseline to CTC Grade $\geq$ 3, Safety Population, CONFIRM Trial

Lab value	Fulvestrant 500 mg (N= 361)				Fulvestrant 250 mg (N=374)			
	Baseline Grade				Baseline Grade			
	0	1	2	3	0	1	2	3
Post-treatment								
Bilirubin								
Grade 3	1	0	0	0	3	1	0	0
Grade 4	2	0	0	0	0	0	0	0
AST								
Grade 3	1	5	0	0	0	4	7	0
Grade 4	1	0	0	0	0	0	0	0
ALT								
Grade 3	2	0	2	0	0	1	0	0
Grade 4	0	0	0	0	0	0	0	0
Alk Phos								
Grade 3	1	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0

Of these 22 subjects, there were 3 subjects in the fulvestrant 500 mg arm (Subject ID# E0184018, E0175027, and E0240007) and 1 subject in the fulvestrant 250 mg arm (Subject ID# E0100001) who experienced clinically significant increases in AST or ALT associated with a significant increase in total bilirubin. These patients' histories were queried in further detail. Although it is impossible to rule out a contribution of drug-induced liver injury with the available data, all were found to have potential alternative explanations for liver function abnormalities and/or underlying conditions that likely predisposed them to develop liver function abnormalities.

Subject # E0100001 was a 72 year-old woman with an AST of 55 IU/L at baseline and otherwise normal liver function tests. She began Faslodex 250 mg on 09/20/2005. Her AST, ALT, alkaline phosphatase, and total bilirubin rose gradually beginning in 10/2005. She reported abdominal pain beginning in 11/2005, and increasing abdominal girth was

also noted. At the time of study discontinuation in 12/2005, her AST, ALT, alkaline phosphatase, and total bilirubin were elevated, and imaging demonstrated extensive metastases involving the entire liver.

Subject # E0184018 was a 68 year-old woman with normal liver function tests and no visceral metastases at baseline. She began Faslodex 500 mg on 07/24/2006. She remained on Faslodex with stable disease and no adverse events recorded until study day #437, at which time she was noted to have jaundice, hepatomegaly, and grade 3-4 elevations of AST, ALT, alkaline phosphatase, and total bilirubin. She discontinued treatment at the same time due to progressive disease, though it is not documented in the CRF whether liver metastases were noted, and died (b) (6) with cause of death listed as metastatic breast cancer.

Subject # E0175027 was a 57 year-old women with "current" hepatosis and chronic cholecystitis documented at study entry. She also had liver metastases present at study entry. She began Faslodex 500 mg on 07/16/2007 at which time her total bilirubin was 0.5 mg/dL. She was noted to have grade 3 elevation of AST, GGT, alkaline phosphatase deemed not related to study drug study day #29. Treatment was continued. Grade 2 liver dysfunction was reported on study day #55 along with icterus, jaundice, and hepatomegaly. Her total bilirubin was elevated to 28 mg/dL. Progressive disease was documented on imaging on study day #60 with appearance of new liver metastases.

Subject # E0240007 was a 65 year-old woman with a history of hepatopathy and alcoholism at study entry. She began fulvestrant 500 mg on 10/30/2006 with baseline grade 1 hepatic cirrhosis listed. She was noted to have grade 1 alcohol poisoning and grade 4 hyperbilirubinemia on study day #59. On study day 85, grade 1 jaundice, hepatomegaly, and cholelithiasis were noted. A right upper quadrant ultrasound was performed on study day #104 (01/22/2007) and demonstrated an enlarged liver with diffusely increased echogenicity and gallstones. There was no intrahepatic biliary ductal dilatation, and there were no metastases seen. The conclusion noted "liver dystrophy—almost incipient liver cirrhosis". She discontinued the study on day #106 (01/24/2007) with persistent hyperbilirubinemia that the investigator deemed unrelated to study drug. The bilirubin was noted to have decreased (though no lab values are available) as of (b) (6) coinciding with the timing of a cholecystectomy approximately (b) (6) after discontinuing treatment. The medical oncologist's notes indicate that decompensation of alcohol-induced cirrhosis was the suspected reason for her persistent hyperbilirubinemia.

In summary, although elevations in liver enzymes occur commonly in association with fulvestrant use, the metastatic cancer population receiving fulvestrant often has alternative explanations for liver function abnormalities or medical conditions that may predispose to liver function abnormalities. For the purposes of this supplemental NDA

evaluating a dose change of fulvestrant from 250 mg to 500 mg monthly, abnormalities of liver function do not demonstrate a clear pattern of dose-dependence.

See also Section 7.4.2 for a discussion of liver function abnormalities in the pooled safety dataset.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The percentage of patients who experienced at least one AE in the CONFIRM trial was slightly higher in the fulvestrant 500 mg arm (67.3% versus 64.2%). The most commonly reported adverse events in the fulvestrant 500 mg arm were injection site pain (11.6%), nausea (9.7%), and bone pain (9.4%). In the fulvestrant 250 mg arm, the most common adverse events were nausea (13.6%), back pain (10.7%), and injection site pain (9.1%). Table 16 below shows adverse events regardless of grade occurring in ≥ 5% of subjects in the fulvestrant 500 mg arm of the CONFIRM trial safety population.

Table 16: Common Adverse Events (≥ 5% in Either Arm), Safety Population, CONFIRM Trial

Adverse Event	Fulvestrant 500 mg (N=361)		Fulvestrant 250 mg (N=374)	
	N	%	N	%
Overall	**243**	**67.3**	**240**	**64.2**
Injection site pain	42	11.6	34	9.1
Nausea	35	9.7	51	13.6
Bone pain	34	9.4	28	7.5
Arthralgia	29	8.0	29	7.8
Headache	28	7.8	25	6.7
Back pain	27	7.5	40	10.7
Fatigue	27	7.5	24	6.4
Pain in extremity	25	6.9	26	7.0
Hot flush	24	6.6	22	5.9
Vomiting	22	6.1	21	5.6
Anorexia	22	6.1	14	3.7
Asthenia	21	5.8	23	6.1
Musculoskeletal pain	20	5.5	12	3.2
Cough	19	5.3	20	5.3

Adverse Event	Fulvestrant 500 mg (N=361)		Fulvestrant 250 mg (N=374)	
	N	%	N	%
Constipation	18	5.0	13	3.5
Dyspnea	16	4.4	19	5.1

†Individual percentages do not add up to overall percentages because some patients experienced more than one adverse event.

7.4.2 Laboratory Findings

Elevation of liver enzymes is a known adverse reaction associated with fulvestrant that was observed in the CONFIRM trial, as well as the pooled safety population of the CONFIRM, NEWEST, FINDER 1, and FINDER 2 trials. In the pooled data, there were post-baseline increases in AST to CTC grade ≥1 observed in 18.8% and 19.2% of subjects receiving fulvestrant 500 mg versus 250 mg, respectively. Post-baseline increases in AST to CTC grade ≥ 3 were observed in 1.6% and 2.3% of subjects receiving fulvestrant 500 mg versus 250 mg, respectively. Post-baseline increases in ALT to CTC grade ≥1 were observed in 16.7% and 16.5% of subjects receiving fulvestrant 500 mg versus 250 mg, respectively. Post-baseline increases in ALT to CTC grade ≥ 3 were observed in 0.8% and 0.6% of subjects receiving fulvestrant 500 mg versus 250 mg, respectively. These data are shown in Table 17 below.

Table 17: Incidence of Changes in Liver Function Parameters from Baseline, Safety Population, Pooled Data

Laboratory parameter Max post-baseline CTC grade	Fulvestrant 500 mg N=560 N (%)	Fulvestrant 250 mg N=567 N (%)
ALT	N=508	N=516
Grade 1	69 (13.6)	68 (13.2)
Grade 2	12 (2.4)	14 (2.7)
Grade 3	4 (0.8)	3 (0.6)
Grade 4	0	0
Total with increase ≥ 1 grade	**85 (16.7)**	**85 (16.5)**
AST	N=505	N=511
Grade 1	77 (15.2)	67 (13.1)
Grade 2	10 (2.0)	19 (3.7)
Grade 3	7 (1.4)	12 (2.3)
Grade 4	1 (0.2)	0
Total with increase ≥ 1 grade	95 (18.8)	98 (19.2)
Alkaline phosphatase	N=511	N=519
Grade 1	66 (12.9)	61 (11.8)

Grade 2	21 (4.1)	26 (5.0)
Grade 3	7 (1.4)	11 (2.1)
Grade 4	0	0
Total with increase ≥ 1 grade	94 (18.4)	98 (18.9)

Reviewer Note: Liver function parameter abnormalities were observed in the CONFIRM trial and the pooled safety data at a much higher incidence than is reflected in the Sponsor's proposed product labeling but did not appear to be dose-dependent. This may reflect use of the adverse events datasets from prior trials rather than the laboratory datasets to determine the incidence of liver function abnormalities in the original product labeling given that many investigators do not report abnormal laboratory values as adverse events. Of note, the current EU labeling of fulvestrant lists elevated liver function tests as a "very common adverse event."

Grade 3 and 4 transaminitis occurred in approximately 1-2% of subjects and did not demonstrate dose-dependence.

The liver function abnormality data from the pooled safety population analysis have been incorporated into the proposed product labeling.

See also Section 7.3.5 for a more detailed analysis of cases of serious liver function abnormalities in the CONFIRM trial.

There were no meaningful differences between fulvestrant doses in terms of other chemistry or hematology parameters.

7.4.3 Vital Signs

There were no clinically meaningful differences in vital signs between treatment arms. There were no clinically meaningful differences in mean blood pressure between the 250 mg and 500 mg fulvestrant arms from baseline to study withdrawal. There was one death in a subject in the 250 mg fulvestrant arm following an adverse event of hypertension that occurred approximately 8 weeks after initiating treatment. A narrative for this case can be found in Section of the review.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were performed at baseline but were not repeated during the study unless clinically indicated.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not applicable in the metastatic cancer population for whom fulvestrant is indicated.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was no convincing evidence of clinically meaningful dose dependency for adverse events. See Sections 7.3 and 7.4 for additional information.

7.5.2 Time Dependency for Adverse Events

No time dependency for adverse events was noted.

7.5.3 Drug-Demographic Interactions

All patients enrolled in the trial were postmenopausal women. More than 96% of subjects enrolled were Caucasian. The demographics of the enrolled population make it impossible to comment on the effect of race or gender on fulvestrant activity.

7.5.4 Drug-Disease Interactions

From the approved Faslodex label:

"In the advanced breast cancer trials, fulvestrant concentrations in women with estimated creatinine clearance as low as 30 mL/min were similar to women with normal creatinine."

"Fulvestrant is metabolized primarily in the liver… (b) (4)

(b) (4)

(b) (4) Safety and efficacy have not been evaluated in patients with moderate to severe hepatic impairment."

7.5.5 Drug-Drug Interactions

From the approved Faslodex label:

"There are no known drug-drug interactions. Fulvestrant does not significantly inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2C19, 2D6, and 3A4 *in vitro*, and studies of co-administration of fulvestrant with midazolam indicate that therapeutic doses of fulvestrant have no inhibitory effects on CYP 3A4 or alter blood levels of drug metabolized by that enzyme. Although fulvestrant is partly metabolized by CYP 3A4, a clinical study with rifampin, an inducer of CYP 3A4, showed no effect on the pharmacokinetics of fulvestrant. Also results from a healthy volunteer study with ketoconazole, a potent inhibitor of CYP3A4, indicated that ketoconazole had no effect on the pharmacokinetics of fulvestrant and dosage adjustment is not necessary in patients co-prescribed CYP 3A4 inhibitors or inducers."

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

From the approved Faslodex label:

"A two-year carcinogenesis study was conducted in female and male rats, at intramuscular doses of 15 mg/kg/30 days, 10 mg/rat/30 days and 10 mg/rat/15 days. These doses correspond to approximately 1-, 3-, and 5-fold (in females) and 1.3-, 1.3-, and 1.6-fold (in males) the systemic exposure [AUC0-30 days] achieved in women receiving the recommended dose of 250 mg/month. An increased incidence of benign ovarian granulosa cell tumors and testicular Leydig cell tumors was evident, in females dosed at 10 mg/rat/15 days and males dosed at 15 mg/rat/30 days, respectively. Induction of such tumors is consistent with the pharmacology-related endocrine feedback alterations in gonadotropin levels caused by an antiestrogen.

Fulvestrant was not mutagenic or clastogenic in multiple *in vitro* tests with and without the addition of a mammalian liver metabolic activation factor (bacterial mutation assay in strains of Salmonella typhimurium and Escherichia coli, *in vitro* cytogenetics study in human lymphocytes, mammalian cell mutation assay in mouse lymphoma cells and *in vivo* micronucleus test in rat)."

7.6.2 Human Reproduction and Pregnancy Data

Faslodex is Pregnancy Category D.

From the approved Faslodex label:

"In female rats, fulvestrant administered at doses ≥ 0.01 mg/kg/day (approximately one-hundredth of the human recommended dose based on body surface area [BSA]), for 2 weeks prior to and for 1 week following mating, caused a reduction in fertility and embryonic survival. No adverse effects on female fertility and embryonic survival were evident in female animals dosed at 0.001 mg/kg/day (approximately one-thousandth of the human dose based on BSA). Restoration of female fertility to values similar to controls was evident following a 29-day withdrawal period after dosing at 2 mg/kg/day (twice the human dose based on BSA). The effects of fulvestrant on the fertility of female rats appear to be consistent with its antiestrogenic activity. The potential effects of fulvestrant on the fertility of male animals were not studied but, in a 6-month toxicology study, male rats treated with intramuscular doses of 15 mg/kg/30 days, 10 mg/rat/30 days, or 10 mg/rat/15 days fulvestrant showed a loss of spermatozoa from the seminiferous tubules, seminiferous tubular atrophy, and degenerative changes in the epididymides. Changes in the testes and epididymides had not recovered 20 weeks after cessation of dosing. These fulvestrant doses correspond to approximately 2-, 3-, and 3-fold the systemic exposure [AUC0-30 days] achieved in women.

In studies in female rats at doses ≥ 0.01 mg/kg/day (IM; approximately one-hundredth of the human recommended dose based on body surface area [BSA]), fulvestrant caused a reversible reduction in female fertility, as well as effects on embryo/fetal development consistent with its antiestrogenic activity. Fulvestrant caused an increased incidence of fetal abnormalities in rats (tarsal flexure of the hind paw at 2 mg/kg/day IM; twice the human dose on BSA) and non-ossification of the odontoid and ventral tubercle of the first cervical vertebra at doses ≥ 0.1 mg/kg/day IM (approximately one-tenth of the human dose on BSA) when administered during the period of organogenesis. Rabbits failed to maintain pregnancy when dosed with 1 mg/kg/day fulvestrant IM (twice the human dose on BSA) during the period of organogenesis. Further, in rabbits dosed at 0.25 mg/kg/day (about one-half the human dose on BSA), increases in placental weight and post-implantation loss were observed, but there were no observed effects on fetal development. Fulvestrant was associated with an increased incidence of fetal variations in rabbits (backwards displacement of the pelvic girdle, and 27 pre-sacral vertebrae at 0.25 mg/kg/day IM; one-half the human dose on BSA) when administered during the period of organogenesis. Because pregnancy could not be maintained in the rabbit following doses of fulvestrant of 1 mg/kg/day and above, this study was inadequate to fully define the possible adverse effects on fetal development at clinically relevant exposures.

Fulvestrant is found in rat milk at levels significantly higher (approximately 12-fold) than plasma after administration of 2 mg/kg. Drug exposure in rodent pups from fulvestrant-treated lactating dams was estimated as 10% of the administered dose. It is not known if fulvestrant is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from FASLODEX in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother."

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable as postmenopausal breast cancer does not occur in pediatric populations.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

From the approved Faslodex label:

"Animal studies have shown no effects other than those related directly or indirectly to antiestrogen activity with intramuscular doses of fulvestrant higher than the recommended human dose. There is no clinical experience with overdosage in humans. No adverse effects were seen in healthy male and female volunteers who received intravenous fulvestrant, which resulted in peak plasma concentrations at the end of the infusion that were approximately 10 to 15 times those seen after intramuscular injection."

There is no potential for abuse.

7.7 Additional Submissions / Safety Issues

Four Month Safety Update: The four-month safety update was submitted electronically by the Sponsor on 03-10-2010 and provided updated information on SAEs and deaths recorded following the original data cut-off date of 02-28-2009 to the 4 month safety update data cut-off date of 10-30-2009. There were 4 additional patient deaths recorded, all of which were attributed to disease progression and occurred in patients who had previously discontinued fulvestrant due to documented disease progression one or more months prior to death. One patient death due to progression was preceded by an adverse event of lower respiratory infection, deemed unrelated to study drug. No new safety issues were identified.

8 Postmarket Experience

No new postmarketing data of relevance to this supplement have been reported.

9 Appendices

9.1 Literature Review/References

Not applicable.

9.2 Labeling Recommendations

The clinical team recommended to the Sponsor [redacted] These labeling recommendations were discussed by the review team and the Sponsor in a teleconference on 07/26/2010 [redacted] FDA concluded that the Sponsor's request to approve a single labeled dose of 500 mg monthly with an additional dose of 500 mg on day #14 was acceptable.

Per clinical pharmacology, a dose of 250 mg monthly with [redacted] an additional 250 mg dose on day #15 of the first cycle was recommended for patients with moderate hepatic impairment (Child-Pugh Class B). There are no data to support the safe use of fulvestrant in patients with severe hepatic impairment (Child-Pugh Class C).

The labeling should be updated to communicate that liver function abnormalities, which are generally grade 1 or 2 elevations in transaminases or alkaline phosphatase, occur in approximately 15% of patients in association with fulvestrant use. Grade ≥ 3 abnormalities of liver function occur in up to 2% of subjects. These liver function abnormalities do not demonstrate dose-dependence.

The labeling should be updated to recommend that fulvestrant be used with caution in patients who are receiving anticoagulants or who have thrombocytopenia rather than stating that the fulvestrant is contraindicated, comparable to the EMA-approved labeling of fulvestrant. A Pubmed search by this reviewer identified no case reports of bleeding complications following treatment with fulvestrant in patients with thrombocytopenia or anticoagulant use despite a theoretical increase in risk of bleeding for such patients.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

TANYA M PROWELL
08/30/2010

AMNA IBRAHIM
08/30/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s012

CHEMISTRY REVIEW(S)

Chemistry Review:	**1. Division:**	**2. NDA Number:**
# 1	ONDQA Div IV HFD - 150	21-344

3. Name and Address of Applicant:	**4. Supplement(s):** Prior Approval **Number:** S 012 **Date(s):** Letter Date: 11/12/2009 Stamp Date; 11/13/2009 PDUFA Goal: 09/13/2010
AstraZeneca 1800 Concord Pike P.O. Box 8355 Wilmington, DE 19803-8355	

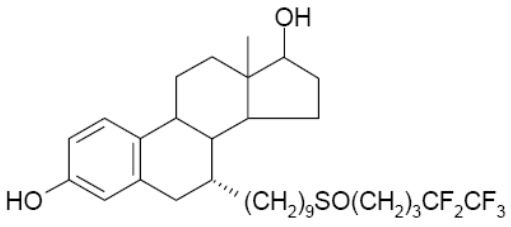
5. Name of Drug:	**6. Nonproprietary name:**
FASLODEX®	Fulvestrant, Injection

7. Supplement Provides for	**8. Amendment(s):**
Safety and efficacy information to support a dose change from the currently approved 250mg dose to a 500mg dose	

9. Pharmacological Category:	**10. How Dispensed:**	**11. Related Documents:**
Indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antistrogen therapy	R_x	

12. Dosage Form:	**13. Potency:**
Injection	250mg and 500mg

14. Chemical Name and Structure:
Fulvestrant: 7-alpha-[9-(4,4,5,5,5-pentafluoropentylsulphinyl) nonyl]estra-1,3,5-(10)- triene-3,17-beta-diol



Fulvestrant
Empirical Formula: $C_{32}H_{47}F_5O_3S$
Molecular Weight: 606.77
CAS Number: 129453-61-8

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be introduced into the aquatic environment is then estimated as 38.7kg annually. The calculated EIC aquatic based on 38.7kg of the unchanged active moiety is 0.00087ppb which is less than the 1ppb requirement. Therefore, the categorical exclusion from the environmental assessment analysis can be granted.

Based on recommendations from the Pharm/Tox Reviewer and the Office of Compliance, and the review of the CMC information provided in this submission, this supplement is recommended for approval from the CMC perspective.

16. Conclusion:

Recommended for approval (AP) from the CMC perspective.

17. Name:	**Signature:**	**Date:**
Hamid Shafiei, Ph.D., Chemist		
18. Concurrence:	**Signature:**	**Date:**
Hasmukh Patel, Ph.D., Branch Chief, Div., VIII, ONDQA		

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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HAMID R SHAFIEI
08/04/2010

HASMUKH B PATEL
08/04/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s012

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	21344
Supplemental application:	S-012
Supporting document/s:	116
Submission date:	11/12/2009
Received date:	11/13/2009
Product:	Faslodex® (fulvestrant)
Indication:	Treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.
Applicant:	AstraZeneca
Review Division:	Division of Drug Oncology Products
Reviewer:	Kimberly Ringgold, PhD
Supervisor/Team Leader:	Haleh Saber, PhD
Division Director:	Robert Justice, MD
Project Manager:	Alberta Davis-Warren

TABLE OF CONTENTS

1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

There are no nonclinical issues to preclude the approval of the supplemental NDA for the proposed dose change

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

Please refer to section 12.1 for labeling recommendations

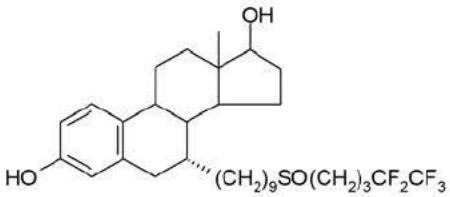
1.2 Brief Discussion of Nonclinical Findings

Nonclinical studies were reviewed by Lilliam Rosario, PhD in 2001. No new studies were submitted with this current application.

2 Drug Information

2.1 Faslodex

2.1.1 CAS Registry Number:	129453-61-8
2.1.2 Generic Name:	fulvestrant
2.1.3 Code Name:	ICI 182,780; ZD9238
2.1.4 Chemical Name:	7-alpha-[9-(4,4,5,5,5-penta fluoropentylsulphinyl) nonyl]estra-1,3,5-(10)- triene-3,17-beta-diol
2.1.5 Molecular Formula/Molecular Weight	$C_{32}H_{47}F_5O_3S$/606.77
2.1.6 Structure	



2.1.7 Pharmacologic class:	estrogen receptor antagonist

2.2 Relevant IND/s, NDA/s, and DMF/s:

None

2.3 Clinical Formulation

2.3.1 Drug Formulation

Qualitative composition of FASLODEX

Components	Quantity % w/v	mg/ml	Function	Standard
Fulvestrant	(b) (4)			
Alcohol	10.0	(b) (4)	Co-solvent	USP
Benzyl alcohol	10.0		Co-solvent	USNF
Benzyl benzoate	15.0		Co-solvent	USP
Castor oil	To 100		Co-solvent and release rate modifier	USP

2.3.2 Comments on Novel Excipients

None

2.3.3 Comments on Impurities/Degradants of Concern

(b) (4)

(b) (4)

2.4 Proposed Clinical Population and Dosing Regimen

Patients with hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy

2.5 Regulatory Background

3 Studies Submitted

3.1 Studies Reviewed

No new studies submitted

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

Review of NDA 21344 completed in 2001 by Dr. Lilliam Rosario

11 Integrated Summary and Safety Evaluation

FASLODEX® is an estrogen receptor antagonist that binds to the estrogen receptor with comparable affinity to that of estradiol. This supplemental NDA was submitted to support a dose change from the currently approved 250 mg dose to a 500 mg dose. FASLODEX® is currently approved for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. The pharmacology and toxicology profiles of FASLODEX® have been reviewed by Dr. Lilliam Rosario in 2001. Sufficient nonclinical and/or clinical data exist to support the safety of Faslodex for the proposed 500 mg dose.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

KIMBERLY R RINGGOLD
09/03/2010

HALEH SABER
09/03/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s012

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES-TEAM LEADER'S MEMO

NDA/Serial Number:	21-344 / S012
Drug Name:	Faslodex® (fulvestrant) Injection
Indication(s):	Treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy
Applicant:	AstraZeneca
Date(s):	Submission Date: November 13, 2009 PDUFA Date: September 13, 2010
Review Priority:	Standard
Biometrics Division:	DBV
Statistical Reviewer:	Xiaoping (Janet) Jiang, Ph.D.
Secondary Reviewer:	Shenghui Tang, Ph.D., Team Leader
Concurring Reviver:	Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Division of Drug Oncology Product (HFD-150)
Clinical Team:	Tatiana Prowell, M.D., Clinical Reviewer Amna Ibrahim, M.D., Deputy Division Director
Project Manager:	Alberta Davis-Warren

Keywords: Log-rank test, Breast Cancer, Progression Free Survival, Time To Progression, Overall Survival

Faslodex is currently indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. In this NDA supplement submission, the applicant submitted safety and efficacy information to support a dose change from the currently approved 250 mg dose to 500 mg dose. The pivotal study in this submission was a randomized, double-blind, parallel-group, multicenter, phase III study (D6997C00002) to compare 2 dose levels (500 mg vs. 250 mg) of fulvestrant in postmenopausal women with oestrogen receptor positive (ER+) advanced breast cancer who had either relapsed whilst on adjuvant endocrine therapy, or progressed whilst on first endocrine therapy for advanced disease. For further details regarding the design, data analyses, and results of this phase 3 study, please refer to the statistical review by Dr. Xiaoping (Janet) Jiang (August 12, 2010).

The results from the pivotal study demonstrated that the fulvestrant 500 mg had statistically significant prolongation of the time to progression (TTP, including death from any cause) compared to the currently approved dose of fulvestrant 250 mg. The estimated median TTP was 6.5 months for the treatment with fulvestrant 500 mg versus 5.4 months for the treatment with fulvestrant 250 mg (log-rank p-value=0.0063) with hazards ratio (HR) of 0.80 (95% CI: 0.68; 0.94) in favor of the treatment with fulvestrant 500 mg. Overall survival (OS) was one of the secondary endpoints in the pivotal study. The estimated medians of OS were 25.1 months for the treatment with fulvestrant 500 mg and 22.8 months for the treatment with fulvestrant 250 mg with hazards ratio (HR) of 0.84 (95% CI: 0.70; 1.03).

This team leader concurs with the recommendations and conclusions of the statistical reviewer (Dr. Xiaoping (Janet) Jiang) of this application. Whether the marginal improvement (difference in median of 1.1 month) in TTP with no improvement in OS or objective response rate is clinically meaningful and the inference regarding favorable benefit-risk profile for the use of 500 mg dosage of fulvestrant in the replacement of currently approved dosage (250 mg) is deferred to the clinical review team.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

SHENGHUI TANG
08/17/2010

RAJESHWARI SRIDHARA
08/17/2010

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	21-344 / S012
Drug Name:	Faslodex® (fulvestrant) Injection
Indication(s):	Treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy
Applicant:	AstraZeneca
Date(s):	Submission Date: November 13, 2009 PDUFA Date: September 13, 2010
Review Priority:	Standard
Biometrics Division:	DBV
Statistical Reviewer:	Xiaoping (Janet) Jiang, Ph.D.
Concurring Reviewers:	Shenghui Tang, Ph.D., Team Leader Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Division of Drug Oncology Product (HFD-150)
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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

Faslodex is currently indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. In this NDA supplement submission, the applicant submitted safety and efficacy information to support a dose change from the currently approved 250 mg dose to 500 mg dose. The pivotal study in this submission was a randomized, double-blind, parallel-group, multicenter, phase III study (D6997C00002) to compare 2 dose levels (500 mg vs. 250 mg) of fulvestrant in postmenopausal women with oestrogen receptor positive (ER+) advanced breast cancer who had either relapsed whilst on adjuvant endocrine therapy, or progressed whilst on first endocrine therapy for advanced disease. The results from the pivotal study demonstrated that the fulvestrant 500 mg had statistically significant prolongation of the time to progression (TTP, including death from any cause) compared to the currently approved dose of fulvestrant 250 mg. The estimated median TTP was 6.5 months for the treatment with fulvestrant 500 mg versus 5.4 months for the treatment with fulvestrant 250 mg (log-rank p-value=0.0063) with hazards ratio (HR) of 0.80 (95% CI: 0.68; 0.94) in favor of the treatment with fulvestrant 500 mg. Overall survival (OS) was one of the secondary endpoints in the pivotal study. The estimated medians of OS were 25.1 months for the treatment with fulvestrant 500 mg and 22.8 months for the treatment with fulvestrant 250 mg with hazards ratio (HR) of 0.84 (95%CI: 0.70; 1.03). Whether the marginal improvement (difference in median of 1.1 month) in TTP with no improvement in OS or objective response rate is clinically meaningful and the inference regarding favorable benefit-risk profile for the use of 500 mg dosage of fulvestrant in the replacement of currently approved dosage (250 mg) is deferred to the clinical review team.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In this sNDA submission, efficacy data of Faslodex were collected from a pivotal study D6997C00002 and 2 supportive studies D6997C00004 and D6997C00006. For simplicity, the last 3 digits of each study ID will be used to represent each of these 3 studies throughout the whole review. The definition of TTP in the pivotal study was actually the conventional term of progression free survival (PFS). For convenience, the term of PFS, instead of TTP, will be used through the whole review. This review only focused on the pivotal study 002.

Study 002 was a randomized, double-blind, parallel-group, multicenter, phase III study to compare 2 dose levels (250 mg vs. 500 mg) of fulvestrant in postmenopausal women with oestrogen receptor positive (ER+) advanced breast cancer who had either relapsed whilst on adjuvant endocrine therapy, or progressed whilst on first endocrine therapy for advanced disease. It was conducted in 128 centers in 17 countries. Besides USA, Mexico, Belgium, Italy and Spain, most countries were in Asia, East Europe, and South America. A total of 736 postmenopausal women with histological/cytological confirmation of ER+ breast cancer who had relapsed or progressed on previous endocrine therapy were randomized into this study. The primary endpoint of Study 002 was PFS. The primary analysis of PFS was an unstratified log-rank test.

Study 004 was a randomized, double-blind, parallel-group, multicenter study. This study was conducted at 43 centers in Japan. A total of 143 Japanese patients were randomized 1:1:1 to

receive either fulvestrant 250 mg; fulvestrant 250mg (plus 250 mg loading regimen), referred to hereafter as fulvestrant 250 mg + LD; or fulvestrant 500 mg. The primary endpoint of Study 004 was objective response rate (ORR).

Study 006 was a randomized, double-blind, parallel-group, multicenter study. The target population was postmenopausal women with oestrogen receptor (ER) positive advanced breast cancer who had either: relapsed whilst on adjuvant endocrine therapy; or disease within 12 months after completion of adjuvant therapy. This study was conducted at 34 centers in 8 countries, including Belgium, Canada, France, Turkey, and other East Europe countries. A total of 144 patients were randomized 1:1:1 to receive either fulvestrant 250 mg; fulvestrant 250mg (plus 250 mg loading regimen), referred to hereafter as fulvestrant 250 mg + LD; or fulvestrant 500 mg. The primary endpoint in Study 006 was objective response rate (ORR).

1.3 ISSUES AND FINDINGS

Issues:

- In Study 002, there were 235 patients (31.9% of all randomized patients) who had non-measurable disease at the baseline. Among these patients, 185 PFS events occurred (one PFS event was corresponding to one patient). One hundred seventy-two (93%) of these 185 PFS events were progression disease (PD). Among the 172 PD events, there were 14 (8%) PD events (10 in 500 mg arm and 4 in 250 mg arm) that were either not confirmed (for one patient) or were confirmed by an unacceptable imaging modality. Although the study was double-blinded, this imbalance in the study conduct might introduce bias in the estimate the treatment effect. This reviewer has performed several sensitivity analyses by either excluding or censoring PFS at the dates of PD for these 14 non-measurable disease patients whose PD status were either not confirmed or confirmed by an unacceptable imaging modality. The results of these sensitivity analyses are consistent with the primary analysis results of PFS.

- There were only 31 (4%) of U.S patients enrolled in the pivotal study 002. The under-representation of U.S. population would bring a concern that whether the results of the pivotal study could be extrapolated into the U.S. population.

Findings

- The PFS results from the pivotal study demonstrate that the treatment of fulvestrant 500 mg has statistically significant improvement in PFS compared to treatment of fulvestrant 250 mg. As shown in the following Table A, the estimated median PFS is 6.5 months for the treatment with fulvestrant 500 mg versus 5.4 months for the treatment with fulvestrant 250 mg (log-rank p-value=0.0063) with hazards ratio (HR) of 0.80 (95% CI: 0.68; 0.94) in favor of the treatment with fulvestrant 500 mg.

Table A. Results of PFS in Study 002 (ITT Population)

	Fulvestrant 500 mg (N=362)	**Fulvestrant 250 mg (N=374)**
Number Censored (%)	77 (21.3)	65 (17.4)
Events (%)	285 (78.7)	309 (82.6)
Death (%)	25 (8.8)	24 (7.8)
PD (%)	260 (91.2)	285(92.2)
Median PFS in Months (95% CI)	6.5 (5.5; 8.3)	5.4 (3.8; 5.9)
Log-rank p-value	0.0063	
Hazard Ratio* (95% CI)	0.80 (0.68, 0.94)	

** A hazard ratio of less than 1 indicates that the treatment of Fulvestrant 500 mg is associated with less risk of progression or death compared to Fulvestrant 250 mg.*

- As shown in the following Table B, the results of OS, one of the secondary endpoints in Study 002, show a trend in favor of the treatment with fulvestrant 500 mg.

Table B. Results of Overall Survival in Study 002 (ITT)

	Fulvestrant 500 mg (N=362)	**Fulvestrant 250 mg (N=374)**
Number Censored (%)	187 (51.7)	171 (45.7)
Number of Deaths (%)	175 (48.3)	203 (54.3)
Median OS in Months (95% CI)	25.1 (22.9, 30.4)	22.8 (19.5, 27.5)
Log-rank p-value	0.091	
Hazard Ratio (95% CI)	0.84 (0.70, 1.03)	

**A hazard ratio of less than 1 indicates that the treatment of Fulvestrant 500 mg is associated with less risk of death compared to Fulvestrant 250 mg.*

2 INTRODUCTION

2.1 OVERVIEW

Faslodex is currently indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. The approved dose with current indication is 250 mg. The approval of current indication with dose of 250 mg was based on showing non-inferiority in overall response rate compared to an active control treatment. In this NDA supplement submission, the applicant submitted safety and efficacy information to support a dose change from the approved dose of 250 mg to 500 mg. The data were collected from the pivotal study D6997C00002 with two supportive studies D6997C00004 and D6997C00006.

2.2 DATA SOURCES

Data used for this review were from the electronic submission received on November 13, 2009. The network paths were "\\Cdsesub1\evsprod\NDA0213447\0005".

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

This section mainly focuses on efficacy evaluation for the pivotal study 002. It will provide the description and results of the study based on the protocol; the statistical analysis plan (SAP) and the clinical study report (CSR). Any difference between the CSR and the protocol or SAP will be discussed in this section.

3.1.1 STUDY OBJECTIVE

The primary objective of Study 002 was to compare the efficacy of fulvestrant 500 mg treatment with fulvestrant 250 mg treatment in terms of time to progression (TTP).

The followings are selected secondary objectives of Study 002.

- To compare the objective response rate (ORR) of patients treated with fulvestrant 500 mg with the objective response rate of patients treated with fulvestrant 250 mg
- To compare clinical benefit rate (CBR) of patients treated with fulvestrant 500 mg with the clinical benefit rate of patients treated with fulvestrant 250 mg
- To compare duration of response (DoR) of patients treated with fulvestrant 500 mg with the duration of response of patients treated with fulvestrant 250 mg
- To compare the overall survival (OS) of patients treated with fulvestrant 500 mg with the overall survival of patients treated with fulvestrant 250 mg

3.1.2 STUDY DESIGN

Pivotal study 002 was a randomized, double-blind, parallel-group, multicenter, phase III study to compare 2 dose levels of fulvestrant in postmenopausal women with oestrogen receptor positive (ER+) advanced breast cancer who had either relapsed whilst on adjuvant endocrine therapy, or progressed whilst on first endocrine therapy for advanced disease. A total of 736 patients were randomized 1:1 to the following groups:

- Fulvestrant 500 mg intramuscularly (im) every 28 (±3) days plus an additional 500 mg on Day 14 (±3) of first month only
- Fulvestrant 250 mg im every 28 (±3) days

Treatment was to continue until disease progression occurred, unless any of the criteria for treatment discontinuation were met first. All patients were to be followed up for disease progression and survival, regardless of whether they had discontinued randomized treatment, unless they had withdrawn consent.

The primary endpoint PFS was assessed by objective tumor assessments every 12 weeks using RECIST except for the patients with bone only disease.

3.1.3 EFFICACY ENDPOINTS

3.1.3.1 Primary Endpoint

The primary endpoint in Study 002 was time to progression (TTP). TTP was defined as the time between the date of randomization and the date of earliest evidence of disease progression (including death from any cause). From the definition of TTP, the primary endpoint TTP is actually conventional term of progression free survival (PFS). As mentioned in the beginning of the review, the term of TTP has been replaced by PFS through the whole review. If a patient had no disease assessment at all, then PFS were censored on the date of randomization. If the patient was not known to have progressed or died at the time of the data cutoff date (regardless of whether the patient was still being followed for progression or was lost to follow-up), then PFS was censored at date of last evaluable disease assessment per RECIST. The date of progression was the date of the investigation/procedure (imaging, biopsy, etc) that led to the diagnosis of progression. If more than one investigation/procedure was performed, and assuming that more than one confirms progression, the date of progression was the date of the earliest assessment from the visit at which the visit response was PD. Per the study protocol, the definition of progression for patients without measurable disease at baseline was defined as having ≥ 1 new lytic bone lesion(s), ≥ 1 new lesion(s) outside of the bone, or unequivocal progression of existing bone lesions.

Reviewer's Comments:

[1] As stated in the meeting minutes of pre-sNDA meeting held on 17 June 2009, FDA provided recommendation regarding to the primary analysis of PFS. The recommendation are quoted as follows:

"PFS data should be censored on the date of the last tumor assessment documenting absence of progression for patients:

- Who were alive, on study and progression-free at the time of the analysis
- Who were given/changed therapy other than the study treatment prior to observing progression
- Who discontinued (due to personal preference or toxicity)/ withdrew or lost to follow-up
- For whom documentation of disease progression or death occurred after ≥ 2 consecutive missed tumor assessments.

By applying FDA recommended censoring rules, the applicant has conducted a PFS analysis and provided the results in the sNDA submission. These PFS results are considered as the primary analysis results.

3.1.3.2 Secondary Endpoints

In Study 002, secondary efficacy endpoints were objective response rate (ORR), clinical benefit rate (CBR), duration of response (DoR), duration of clinical benefit (DoCB), overall survival (OS) and time to response (TTR). The definitions of the selected endpoints are as follows.

Overall survival (OS) was defined as the time between the randomization and death. Patients, who died, regardless of the cause of death, were considered to have an event. Survival time for a patient who was lost to the follow-up prior to the end of the trial or who was withdrawn from the trial was censored at the time of last contact. Survival time for a patient who was still being treated was censored at the last available date where the patient was known to be alive.

Objective response (OR) was defined as a patient having a best overall response of either CR or PR. A patient has a best overall response of CR or PR if they had an overall response of CR or PR at one visit and this was confirmed as CR or PR by repeat imaging not less than 4 weeks later.

Objective response rate (ORR) was defined as the proportion of all treated patients with measurable disease at baseline who have an objective response.

Duration of response (DoR) was evaluated only for patients who had an OR, and was defined in two different ways:

- **(DoR from response to progression, per RECIST)** from date of first documentation of objective response (ie, the initial visit at which CR or PR was recorded and not the confirmatory visit) until the date of disease progression or death due to any cause (whichever is earlier).

- **(DoR from randomization to progression)** from the date of randomization until the date of disease progression or death due to any cause (whichever is earlier).

3.1.4 SAMPLE SIZE CONSIDERATIONS

Assuming that the primary endpoint PFS followed exponential distribution and median time of PFS for 250 mg fulvestrant in this patient population was estimated to be 5.5 months, approximately 632 events (progression or death events) were required to detect a hazard ratio of 0.8 for 500 mg fulvestrant compared to 250 mg fulvestrant, at a 2-sided significance level of 5%, with 80% power. A hazard ratio of 0.8 would equate to a prolongation in median PFS for 500 mg fulvestrant over 250 mg fulvestrant of 1.38 months (i.e., a median TTP of 6.88 months for 500 mg fulvestrant compared to median PFS of 5.5 months for 250 mg fulvestrant). The required 632 events would be observed approximately 6 months following the end of recruitment if 720 patients were enrolled over a period of 36 months.

Overall Survival analysis were planned to be performed after the proportion of reported deaths exceeds 50% of the total number of patients required. Per protocol, if 50% of deaths occurred before the required 632 progression events then the survival analysis would not be performed until the 632 progression events were observed.

3.1.5 INTERIM ANALYSIS

No interim analysis was planned in Study 002.

Reviewer's Comments:

Although no interim analysis was planned in Study 002, at least 3 times of safety data reviews were conducted by the (b) (4) Per SAP, the first two times of safety data review were conducted for the first 30 and 60 patients. More such safety reviews occurred at approximately 9 month intervals after the second review. At the time of these reviews, the un-blinded data were available only for the members of the (b) (4)

3.1.6 PRIMARY ANALYSES

The primary analysis of the primary endpoint PFS in Study 002 was an unadjusted log-rank test on intent to treatment (ITT) population. The definition of full analysis set (FAS) is the same as ITT. For secondary endpoint OS, the unadjusted log-rank test was performed.

3.1.7 APPLICANT'S RESULTS AND STATISTICAL REVIEWER'S COMMENTS/FINDINGS

This section summarizes the applicant's major efficacy results from Study 002 and provides the statistical reviewer's comments and findings.

3.1.7.1 Disposition of Patients

A total of 736 patients were randomized in Study 002. The following table summarizes the patient disposition.

Table 1: Summary of Patient Disposition

Population	Fulvestrant 500 mg n (%)	Fulvestrant 250 mg n (%)	Total n (%)
Randomized	362 (100)	374 (100)	736 (100)
Not Treated	1 (0.3)	0 (0)	1(0.1)
Received Treatment	361 (99.7)	374 (100)	735 (99.9)
Ongoing any Study Treatment at Data Cut-off	41 (11.4)	31 (8.3)	72 (9.8)
Discontinued Treatment **-Objective Progression of Disease**	320(88.6) 258 (71.5)	343 (91.7) 278 (74.3)	663 (90.2) 536 (72.9)

[Source: Study 002 Clinical Study Report Table 11.1.1]

3.1.7.2 Demographic and Baseline Characteristics

As shown in Tables 2, 3, and 4, the demographic and baseline characteristics appeared to be balanced between the two treatment arms.

Table 2: Summary of Demographic Characteristics (ITT Population)

	Fulvestrant 500 mg N=362	Fulvestrant 250 mg N=374
Race, n (%)		
Caucasian	349 (96.4)	358 (95.7)
Oriental	2 (0.6)	0
Black	2 (0.6)	1 (0.3)
Other	9 (2.5)	15 (4.0)
Age Group		
< 65	218 (60.2)	226 (60.4)
>= 65	144 (39.8)	148 (39.6)
Mean (SD)	61.0 (11.47)	60.8 (11.94)
Median	61.0	61.0
Range	26-91	23-87

[Source: Study 002 Clinical Study Report Table 18]

Table 3: Selected Baseline Characteristics (ITT Population)

Baseline Characteristic	Number (%) of Patients	
	Fulvestrant 500 mg N=362	Fulvestrant 250 mg N=374
Hormone Receptor Status (at primary diagnosis)		
ER+ve	362 (100.0)	374 (100.0)
PgR+ve	241 (66.6)	266 (71.1)
PgR-ve	92 (25.4)	96 (25.7)
PgR unknown	29 (8.0)	12 (3.2)
Disease Characteristics (at randomization)		
Locally advanced breast cancer only	4 (1.1)	11 (2.9)
Metastatic disease	358 (98.9)	363 (97.1)
Any visceral disease	239 (66.0)	232 (62.0)
Bone only	87 (24.0)	77 (20.6)
Measurable Disease		
No	112 (30.9)	113 (30.2)
Yes	240 (66.3)	261 (69.8)

[Source: Study 002 Clinical Study Report Table 9]

Table 4: Selected Baseline Characteristics (ITT Population)

Baseline characteristic	Number (%) of Patients	
	Fulvestrant 500 mg N=362	Fulvestrant 250 mg N=374
Histology Type		
Adenocarcinoma	30 (8.3)	41 (11.0)
Undifferentiated carcinoma	6 (1.7)	7 (1.9)
Infiltrating ductal carcinoma	221 (61.0)	239 (63.9)
Infiltrating lobular carcinoma	55 (15.2)	46 (12.3)
Other	50 (13.8)	41 (11.0)
Tumor Grade		
Well differentiated	24 (6.6)	30 (8.0)
Moderately differentiated	129 (35.6)	125 (33.4)
Poorly differentiated	73 (20.2)	81 (21.7)
Undifferentiated	1 (0.3)	5 (1.3)
Unassessable	21 (5.8)	13 (3.5)
Not done	114 (31.5)	120 (32.1)

[Source: Study 002 Clinical Study Report Table 9]

3.1.7.3 Primary Endpoint

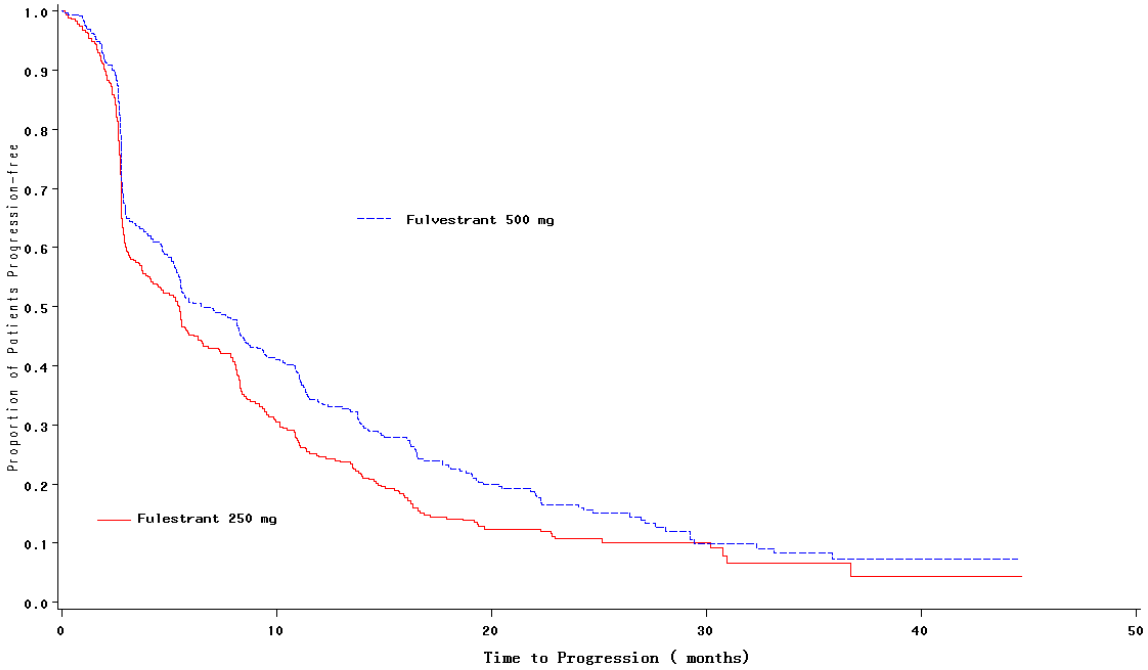
The primary analysis of PFS in Study 002 was log-rank test on ITT population. The PFS results in Table 5 and Kaplan-Meier Curves in the following Figure 1 were obtained by applying FDA recommended censoring rules that were provided in pre-sNDA meeting.

Table 5: Results of PFS in Study 002 (ITT Population)

	Fulvestrant 500 mg (N=362)	Fulvestrant 250 mg (N=374)
Number Censored (%)	77 (21.3)	65 (17.4)
Events (%)	285 (78.7)	309 (82.6)
Death (%)	25 (8.8)	24 (7.8)
PD (%)	260 (91.2)	285(92.2)
Median PFS in Months (95% CI)	6.5 (5.5; 8.3)	5.4 (3.8; 5.9)
Log-rank p-value	0.0063	
Hazard Ratio* (95% CI)	0.80 (0.68, 0.94)	

**A hazard ratio of less than 1 indicates that the treatment of Fulvestrant 500 mg is associated with less risk of progression or death compared to Fulvestrant 250 mg.*

Figure 1: Kaplan-Meier Curves of PFS in Study 002 (ITT)



Reviewer's Comments:

[2] The applicant also provided PFS results that were obtained by applying the censoring rules described in the statistical analysis plan (SAP). Unlike FDA recommended censoring rules, the censoring rules in SAP did not censor PFS for the patients who were given/changed therapy other than the study treatment prior to observing progression or patients whose documentation of disease progression or death occurred after ≥ 2 consecutive missed tumor assessments. The PFS results based on applying censoring rules specified in SAP are consistent with the results of the primary analysis results of PFS with median PFS 6.5 months for Fulvestrant 500 mg versus 5.5 months for Fulvestrant 250 mg (HR=0.80, 95%CI: 0.69; 0.94, log-rank p-value=0.0061).

[3] Since PFS depends on the length of assessment schedule and frequency of assessment, any imbalances in the tumor assessment schedule and frequency between the two arms may introduce systematic bias in the evaluation of PFS. Per protocol, Efficacy for all patients would be assessed by objective tumor assessments every 12 weeks using the RECIST criteria except for those patients with bone only disease. The summary results in the following tables show that there was no imbalance in time from randomization to tumor assessment between two treatment groups.

Table 6: Summary of Time to Progression Assessment (ITT Population)

Time (Months) from Randomization to:	Number (%) of Patients		Mean (SD, months)	
	Fulvestrant 500 mg (N=362)	Fulvestrant 250 mg (N=374)	Fulvestrant 500 mg (N=362)	Fulvestrant 250 mg (N=374)
1st Evaluable RECIST Assessment	349 (96.4)	366 (97.9)	2.8 (0.91)	2.8 (1.48)
2nd Evaluable RECIST Assessment	207 (57.2)	195 (52.1)	5.6 (1.13)	5.5 (0.93)
3rd Evaluable RECIST Assessment	163 (45.0)	147 (39.3)	8.6 (2.17)	8.0 (1.14)
4th Evaluable RECIST Assessment	137 (37.8)	109 (29.1)	11.0 (1.53)	11.0 (3.08)
5th Evaluable RECIST Assessment	110 (30.4)	75 (20.1)	14.0 (2.82)	13.5 (1.49)

Table 7: Summary of Time to Progression Assessment (ITT Population)

Time (Months) from Randomization to:	Median (months)	
	Fulvestrant 500 mg (N=362)	Fulvestrant 250 mg (N=374)
1st Evaluable RECIST Assessment	2.8	2.7
2nd Evaluable RECIST Assessment	5.5	5.5
3rd Evaluable RECIST Assessment	8.3	8.3
4th Evaluable RECIST Assessment	11.0	11.0
5th Evaluable RECIST Assessment	13.8	13.8

Table 8: Time to Progression Assessment (Non-Measurable Patients)

	Number (%) of Patients		Mean (SD, months)		Median (months)	
Evaluable RECIST Assessment	Fulvestrant 500 mg (N=122)	Fulvestrant 250 mg (N=113)	Fulvestrant 500 mg (N=122)	Fulvestrant 250 mg (N=113)	Fulvestrant 500 mg (N=122)	Fulvestrant 250 mg (N=113)
1st	118 (96.7)	109 (96.5)	2.8 (0.75)	3.0 (1.78)	2.78	2.76
2nd	78	58	5.6 (1.085)	5.59 (0.63)	5.55	5.55
3rd	65	45	9.03 (2.13)	8.41 (0.87)	8.38	8.38
4th	51	31	11.55 (1.98)	12.20 (5.09)	11.10	11.04
5th	39	21	14.54 (3.28)	13.88 (1.29)	13.8	13.8

Reviewer's Comments:

[4] Among 736 randomized patients, 235 (32%) patients had non-measurable disease at the baseline. As shown in the following Table 9, the PFS results in this subgroup are consistent with the ITT population. However, compared to ITT population, the difference of median PFS from Fulvestrant 500 mg to Fulvestrant 250 mg in this subgroup is approximately 3 times longer than the one in ITT population. One may ask two questions: 1) Was the treatment effect of Fulvestrant 500 in ITT driven by the subgroup of non-measurable patients? 2) Was the treatment effect of PFS in this subgroup of patients true? Per protocol, the definition of progression disease for patients without measurable disease at baseline was defined as having ≥ 1 new lytic bone lesion(s), ≥ 1 new lesion(s) outside of the bone, or unequivocal progression of existing bone lesions. During the review process, the FDA review team asked the applicant "Were any patients (from the ITT population) with non-measurable disease at baseline classified as PD based solely upon progression on bone scan (i.e. without confirmation by another imaging modality)?" The applicant responded that there was only one patient in Study 002 who was classified as PD based solely upon progression determined by a bone scan. Per the applicant, this patient had non-measurable disease at baseline, and was found to have violated the study inclusion criteria because their baseline disease was also determined solely by bone scan (the protocol stated that any hotspots identified on the bone scan had to be confirmed by MRI, X-ray or CT). However, there were 13 other patients with non-measurable disease at baseline who were classified as PD had confirmation by Ultrasound or physical exams which were not acceptable and not protocol specified imaging modalities to confirm PD status. Among these 13 patients, 10 patients (8 patients in Fulvestrant 500 mg vs. 2 patients in Fulvestrant 250 mg) were confirmed by Ultrasound and 3 patients (2 patients in Fulvestrant 500 mg) were confirmed by physical exams. The PFS results in the following Table 10, 11, 12 and 13 were obtained by either excluding or censoring PFS at the dates of PD for these 14 patients who had non-measurable disease at baseline and did not have confirmation or did not have an acceptable modality to confirm their PD status.

Table 9: Results of PFS in Study 002 (Non-measurable Patients)

	Fulvestrant 500 mg (N=362)	**Fulvestrant 250 mg (N=374)**
Number Censored (%)	28 (22.95)	22 (19.47)
Events (%)	94 (77.05)	91 (80.53)
Death (%)	25 (8.8)	24 (7.8)
PD (%)	90	82
Median PFS in Months (95% CI)	8.5 (6.0, 11.1)	5.6 (3.9, 8.3)
Log-rank p-value	0.0452	
Hazard Ratio* (95% CI)	0.75 (0.56, 0.997)	

Table 10: Results of PFS Sensitivity Analysis (ITT, Censored PFS for 14 Patients Whose PD Status were not Confirmed or Confirmed by an Unacceptable Imaging Modality*)*

	Fulvestrant 500 mg (N=362)	**Fulvestrant 250 mg (N=374)**
Number Censored* (%)	87 (24.0)	69 (18.5)
Events (%)	275	305
Median in Months (95% CI)	7.5 (5.5; 8.5)	5.4 (4.0; 6.3)
Log-rank p-value	0.0030	
Hazard Ratio (95% CI)	0.78 (0.67, 0.92)	

Table 11: Results of PFS Sensitivity Analysis (ITT without the 14 Patients Whose PD Status were not Confirmed or Confirmed by an Unacceptable Imaging Modality)

	Fulvestrant 500 mg (N=352)	**Fulvestrant 250 mg (N=370)**
Number Censored (%)	77 (24.0)	65 (18.5)
Events (%)	275	305
Median in Months (95% CI)	6.1 (5.3; 8.3)	5.4 (3.7; 6.1)
Log-rank p-value	0.0068	
Hazard Ratio (95% CI)	0.78 (0.67, 0.92)	

Table 12: Results of PFS Sensitivity Analysis (Non-measurable Patients, Censored PFS for 14 Patients Whose PD Status were not Confirmed or Confirmed by an Unacceptable Imaging Modality)

	Fulvestrant 500 mg (N=122)	**Fulvestrant 250 mg (N=113)**
Number Censored (%)	38 (31.2)	26 (23.0)
Events (%)	84	87
Median in Months (95% CI)	10.0 (5.9; 12.4)	5.6 (4.0; 8.3)
Log-rank p-value	0.0104	
Hazard Ratio (95% CI)	0.68 (0.50, 0.92)	

Table 13: Results of PFS Sensitivity Analysis (Non-measurable Patients without 14 Patients who's PD Status were not Confirmed or Confirmed by an Unacceptable Imaging Modality)

	Fulvestrant 500 mg (N=112)	Fulvestrant 250 mg (N=109)
Number Censored (%)	28 (25.0)	22 (20.2)
Events (%)	84	87
Median in Months (95% CI)	8.5 (5.7; 11.3)	5.6 (3.0; 8.3)
Log-rank p-value	0.0291	
Hazard Ratio (95% CI)	0.72 (0.53, 0.97)	

3.1.7.4 Secondary Endpoints

In Study 002, overall survival (OS) and objective response rate (ORR) were evaluated as the secondary efficacy endpoints. Per SAP, the pre-specified analysis for overall survival would occur when approximately 50% of patients had died. Table 14 and Figure 2 show the OS results that were based on 378 (51% of randomized patients) death events and the Kaplan-Meier Curves of OS. Another secondary endpoint ORR results are shown in Table 15.

Table 14: Results of Overall Survival in Study 002 (ITT Population)

	Fulvestrant 500 mg (N=362)	Fulvestrant 250 mg (N=374)
Number Censored (%)	187 (51.7)	171 (45.7)
Number of Deaths (%)	175 (48.3)	203 (54.3)
Median OS in Months (95% CI)	25.1 (22.9, 30.4)	22.8 (19.5, 27.5)
Log-rank p-value	0.091	
Hazard Ratio (95% CI)	0.84 (0.70, 1.03)	

** A hazard ratio of less than 1 indicates that the treatment of Fulvestrant 500 mg is associated with less risk of death compared to Fulvestrant 250 mg.*

Figure 2: Kaplan-Meier Curves of Overall Survival in Study 002 (ITT)

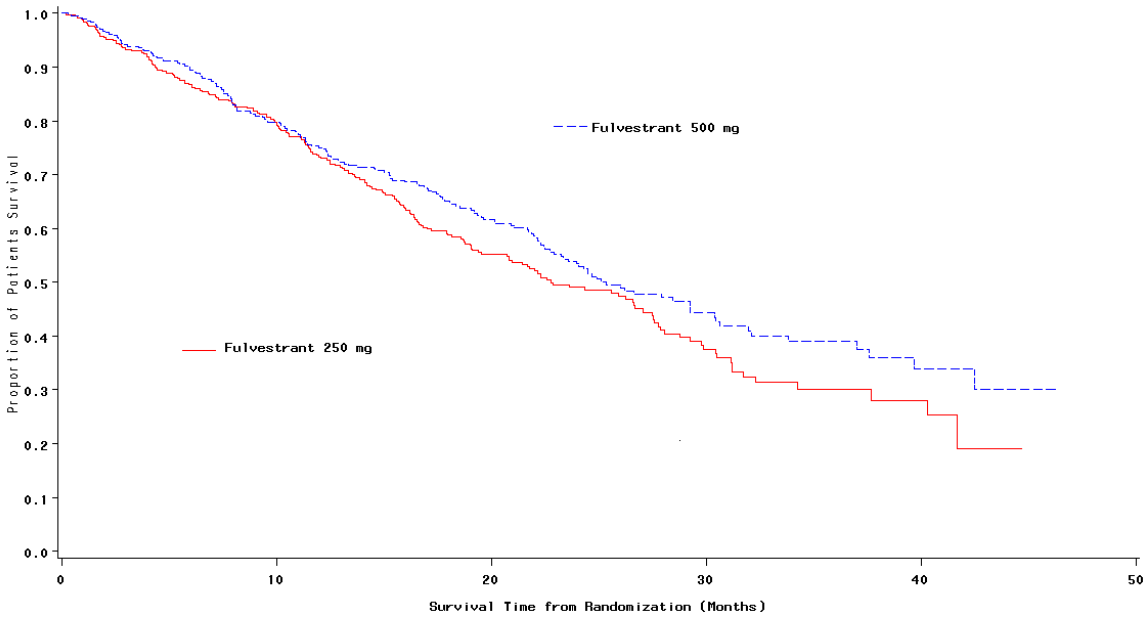


Table 15: Results of Objective Response in Study 002 (Evaluable Patients)

	Fulvestrant 500 mg (N=240)	**Fulvestrant 250 mg (N=261)**
	Number of Patients	
CR	4	1
PR	29	37
CR+PR (%; 95% CI*)	33 (13.8; 9.7-18.8)	38 (14.6; 10.5-19.4)

**CI=Confidence Interval*

Reviewer's Comments:

As shown in Table 15, the results of ORR are not consistent with PFS results since Fulvestrant 250 mg had better observed response rate compared to Fulvestrant 500 mg.

3.2 EVALUATION OF SAFETY

Please refer to the FDA clinical review for safety evaluation of Fulvestrant 500 mg compared to Fulvestrant 250 mg.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section will be focused on the reviewer's results of the exploratory subgroup analyses of the primary endpoint PFS in Study 002.

4.1 GENDER, RACE, AGE AND REGION

The following table shows this reviewer's summary of subgroup analyses in Study 002 based on age and region. Among 736 randomized patients, 368 patients (50.0%) were in East Europe, 444 (60.5%) patients who were less than 65 year old. Since all patients were women and 96% (707) of patients in Study 002 were Caucasian, subgroup analyses by gender and race were not performed.

Table 16: Summary of Subgroup Analyses of PFS

Subgroup	Number of Patients		Hazard Ratio (95% CI)
	Fulvestrant 500 mg (N=362)	Fulvestrant 250 mg (N=374)	
Age			
Age >= 65	144	148	0.84 (0.64, 1.10)
Age <65	218	226	0.77 (0.63, 0.95)
Region			
U.S	15	16	0.37 (0.14, 0.96)
Non-U.S.	347	358	0.82 (0.70, 0.97)
East Europe	183	185	0.75 (0.60, 0.95)
Other	179	189	0.84 (0.67, 1.06)

Reviewer's Comments:

[1] The PFS results in subgroups of patients with age less than 65 year old and patients in East Europe are consistent with the results of ITT population. There were 31 U.S. patients in the pivotal study. As shown in Table 16, the PFS results in the subgroup of US patients seem being favored Fulvestrant 500 mg with small sample size. However, the results of subgroup analyses in Table 16 should be considered as exploratory.

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

Among 736 randomized patients, 235 (32%) of patients whose hormone receptor status were ER positive or PgR positive. This reviewer conducted subgroup analyses on the patients whose hormone receptor status were ER positive or PgR positive and the patients whose hormone receptor status were neither ER positive nor PgR positive. The results of the subgroup analyses are summarized in the following Table 18.

Table 17: Summary of Subgroup Analyses of PFS

Hormone Receptor Status	Number of Patients		Hazard Ratio (95% CI)
	Fulvestrant 500 mg (N=362)	Fulvestrant 250 mg (N=374)	
ER+/PgR+	122	113	0.72 (0.54, 0.97)
Not ER+/PgR+	240	261	0.85 (0.70, 1.03)

Reviewer's Comments:

The results of PFS results in subgroups of patients with ER+ or PgR + are consistent with the results of ITT population. The results of the subgroup analyses in Table 17 should be considered as exploratory.

5 SUMMARY AND CONCLUSIONS

5.1 ISSUES AND FINDINGS

The applicant claimed that the results of the pivotal study demonstrated fulvestrant 500 mg had statistically significant improvement in progression free survival (PFS) compared to the currently approved dose of fulvestrant 250 mg for postmenopausal women with ER-positive advanced breast cancer. After completed review, this reviewer has identified some issues and has the following findings.

Issues:

- In Study 002, there were 235 patients (31.9% of all randomized patients) who had non-measurable disease at the baseline. Among these patients, 185 PFS events occurred (one PFS event is corresponding to one patient). One hundred seventy-two (93%) of these 185 PFS events were progression disease (PD). Among the 172 PD events, there were 14 (8%) PD events (10 in 500 mg arm and 4 in 250 mg arm) that were either not confirmed (one patient) or were confirmed by an unacceptable imaging modality. Although the study was double-blinded, this imbalance in the study conduct might introduce bias in the estimate the treatment effect. This reviewer has performed several sensitivity analyses by either excluding or censoring PFS at the dates of PD for these 14 non-measurable disease patients whose PD status were either not confirmed or not confirmed by an acceptable imaging modality. The results of these sensitivity analyses are consistent with the primary analysis results of PFS.

- There were only 31 (4%) of U.S patients enrolled in the pivotal study 002. The under-representation of U.S. population would bring a concern that whether the results of the pivotal study could be extrapolated into the U.S. population.

Findings

- The PFS results from the pivotal study demonstrate that the treatment of fulvestrant 500 mg has statistically significant improvement in PFS compared to treatment of fulvestrant 250 mg. As shown in the following Table 18, The estimated median PFS is 6.5 months for the treatment with fulvestrant 500 mg versus 5.4 months for the treatment with fulvestrant 250 mg (log-rank p-value=0.0063) with hazards ratio (HR) of 0.80 (95% CI: 0.68; 0.94) in favor of the treatment with fulvestrant 500 mg.

Table 18: Results of PFS in Study 002 (ITT Population)

	Fulvestrant 500 mg (N=362)	**Fulvestrant 250 mg (N=374)**
Number Censored (%)	77 (21.3)	65 (17.4)
Events (%)	285 (78.7)	309 (82.6)
Death (%)	25 (8.8)	24 (7.8)
PD (%)	260 (91.2)	285(92.2)
Median PFS in Months (95% CI)	6.5 (5.5; 8.3)	5.4 (3.8; 5.9)
Log-rank p-value	0.0063	
Hazard Ratio* (95% CI)	0.80 (0.68, 0.94)	

** A hazard ratio of less than 1 indicates that the treatment of Fulvestrant 500 mg is associated with less risk of progression or death compared to Fulvestrant 250 mg.*

- As shown in the following Table 19, the results of OS, one of the secondary endpoints in Study 002 show favorable trend.

Table 19: Results of Overall Survival in Study 002 (ITT Population)

	Fulvestrant 500 mg (N=362)	**Fulvestrant 250 mg (N=374)**
Number Censored (%)	187 (51.7)	171 (45.7)
Number of Deaths (%)	175 (48.3)	203 (54.3)
Median OS in Months (95% CI)	25.1 (22.9, 30.4)	22.8 (19.5, 27.5)
Log-rank p-value	0.091	
Hazard Ratio (95% CI)	0.84 (0.70, 1.03)	

** A hazard ratio of less than 1 indicates that the treatment of Fulvestrant 500 mg is associated with less risk of death compared to Fulvestrant 250 mg.*

5.2 CONCLUSIONS AND RECOMMENDATIONS

The results from the pivotal study D6997C00002 demonstrated that the fulvestrant 500 mg had statistically significant improvement of progression free survival (PFS) compared to the currently approved dose of fulvestrant 250 mg. The estimated median PFS was 6.5 months for the treatment with fulvestrant 500 mg versus 5.4 months for the treatment with fulvestrant 250 mg (log-rank p-value=0.0063) with hazards ratio (HR) of 0.80 (95% CI: 0.68; 0.94) in favor of the treatment with fulvestrant 500 mg. Overall survival (OS) was one of the secondary endpoints in the pivotal study. The estimated medians of OS were 25.1 months for the treatment with fulvestrant 500 mg and 22.8 months for the treatment with fulvestrant 250 mg with hazards ratio (HR) of 0.84 (0.70; 1.03). Whether the magnitude of 1.1 months improvement in median PFS with HR of 0.80 (95% CI: 0.68; 0.94) with no advantage in overall survival or objective response rate can be considered a sufficient evidence of clinical benefit to support approval of 500 mg dosage of fulvestrant in the replacement of currently approved dosage will depend on the favorable risk-benefit ratio and be deferred to the clinical team.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Xiaoping (Janet) Jiang, Ph.D.

Concurring Reviewer: Shenghui Tang, Ph.D., Team Leader
Rajeshwari Sridhara, Ph.D., Division Director

cc:
OODP/DDOP/T. Prowell
OODP/DDOP/A. Ibrahim
OB/DBV/S. Tang
OB/DBV/R. Sridhara
OB/L. Patrician

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

XIAOPING JANET J JIANG
08/12/2010

SHENGHUI TANG
08/13/2010

RAJESHWARI SRIDHARA
08/13/2010

STATISTICS FILING CHECKLIST FOR sNDA21344

NDA Number: 21,344 **Applicant:** AstraZeneca **Stamp Date:** Nov 13, 2009

Drug Name: FASLODEX®(fulvestrant) Injection **NDA Type:** Supplement

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	×			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	×			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	×			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	×			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	×			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	×			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			×	
Appropriate references for novel statistical methodology (if present) are included.			×	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			×	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	×			

STATISTICS FILING CHECKLIST FOR sNDA21344

Reviewing Statistician	Date
Supervisor/Team Leader	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

XIAOPING JANET J JIANG
12/15/2009

KUN HE
12/15/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s012

MICROBIOLOGY/VIROLOGY REVIEW(S)

Product Quality Microbiology Review

19 April 2010

NDA: **21-344/S007 and 21-344/S012**

Drug Product Name
Proprietary: Faslodex Injection
Non-proprietary: fulvestrant

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
01 DEC 2005 (S007)	02 DEC 2005	NA	24 NOV 2009
12 NOV 2009 (S012)	13 NOV 2009	23 NOV 2009	24 NOV 2009

Submission History (for amendments only) – NA

Applicant/Sponsor
Name: AstraZenecxa UK Limited
Address: Alderley Park
Macclesfield Cheshire, SK10 4TG, England
Representative: Nicholas J. Troise
1800 Concord Pike
P.O. Box 8355
Wilmington DE 19803-8355
Telephone: (b) (6)

Name of Reviewer: Denise A. Miller

Conclusion: Approve

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Prior Approval

2. SUBMISSION PROVIDES FOR:
S007 is a labeling amendment
S012 is a dosage change from 250 mg/dose to 500 mg/dose.

3. MANUFACTURING SITE: no change

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:
Dosage form: sterile liquid for injection, prefilled syringes
Route of Administration: Intramuscular
Strength/Potency: 250 mg/5 mL

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: treatment for metastatic breast cancer

B. SUPPORTING/RELATED DOCUMENTS: NA

C. REMARKS:
Supplement 007 was originally submitted to the Agency on 05-DEC-2005. As this supplement had not been closed at the time of Supplement 12 submission, the review of S007 was added.
Supplement 012 was in e-CTD format.

filename: N021344S012R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommend to approve from a quality microbiology standpoint.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - NA

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –
Supplement 007 was a labeling change.
Supplement 012 was a dosage change. The change in the dose required a change (b) (4)

B. Brief Description of Microbiology Deficiencies - None

C. Assessment of Risk Due to Microbiology Deficiencies - NA

III. Administrative

A. Reviewer's Signature _____
Denise A. Miller, Microbiologist

B. Endorsement Block _____
Stephen E. Langille, Ph.D.

C. CC Block
N/A

Product Quality Microbiology Assessment

S-007

Supplement 007 was a labeling amendment dated 01-DEC-2005 (received 05-DEC-2005). A quality microbiology review of the amendment was requested in Dec of 2009. The changes to the labeling included an update to the amount of inactive ingredients, changes to the (b) (4) sections for (b) (4) Populations-Hepatic Impairment, and added to the Adverse Reaction section to include (b) (4) These changes did not have any quality microbiology issues.

S-012

Supplement 012 was an amendment for a dosage change dated 12-NOV-2009 (received 13-NOV-2009). There was no change in the formulation or in the manufacture of the drug product. The drug product remains at 250mg/5 mL in a single use prefilled syringe. The dosage change is from a single 250 mg/5 mL i.m. injection to two 250mg/5mL i.m. injections. Both the single and double injections are in the buttocks.

(b) (4)

-ACCEPTABLE-

No deficiencies noted based on the microbiology information submitted

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-7	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

DENISE A MILLER
04/21/2010

STEPHEN E LANGILLE
04/21/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	21-344/S012
Submission Date:	12 November, 2009
Brand Name:	FASLODEX™
Generic Name:	Fulvestrant
Formulation:	50 mg/mL injection solution
OCP & Pharmacometrics Primary Reviewer:	Young Jin Moon, Ph.D.
Pharmacometrics Secondary Reviewer:	Nitin Mehrotra, Ph.D.
OCP Team Leader:	Julie M. Bullock, Pharm.D.
Pharmacometrics Team Leader:	Christine Garnett, Pharm.D.
OCP Division:	Division of Clinical Pharmacology 5
ORM Division:	Division of Drug Oncology Products
Sponsor:	AstraZeneca
Submission Type; Code:	SE2
Dosing regimen:	500 mg IM injection at intervals of one month with an additional 500 mg dose given two weeks after the initial dose
Indication:	For the treatment of hormone receptor positive metastastic breast cancer in postmenopausal women with disease progression following antiestrogen therapy

Table of contents

1 EXECUTIVE SUMMARY

This is a supplemental NDA for FASLODEX (fulvestrant) which provides safety and efficacy information to support a dose change from the currently approved monthly 250 mg dose to a monthly 500 mg dose plus an additional 500 mg dose given two weeks after the initial dose (500 mg + AD). The proposed indication for fulvestrant 500 mg + AD is the same as the currently approved indication for fulvestrant 250 mg.

Data from two supporting phase 2 trials (FINDER 1 and FINDER 2) were available for the population pharmacokinetic analysis of fulvestrant. These studies assessed the PK of fulvestrant in patients treated one of the following dose regimens of FASLODEX:

- 250 mg: 250 mg at intervals of one month
- 250 mg + AD: 500 mg on Day 1; 250 mg on Days 15, 29, and monthly thereafter
- 500 mg + AD: 500 mg on Days 1, 15, 29 and monthly thereafter

The sponsor's proposed label changes for the new 500 mg regimen were based on the population PK analysis. The sparse data were analyzed using a non-linear mixed effects approach. A two-compartment model with a first order absorption and first order elimination process was fitted to the combined data obtained from FINDER 1 and FINDER 2. The additional 500 mg dose of FASLODEX given on Day 15 causes plasma levels to reach close to steady state within first month of dosing. The pharmacokinetics of fulvestrant appeared to be linear across the dosing regimens studied.

In addition, in this supplement the applicant incorporated the results from the hepatic impairment study (Study 0063; Submission Date 12/1/05) which was reviewed by Dr. Sophia Abraham (DARRTS communication date 2/26/07). Dr. Abraham stated in her review that a dose of 250 mg given once a month could be administered to patients with moderate hepatic impairment (Child-Pugh B), even though the mean AUC of fulvestrant increased by 70% compared to those with normal hepatic function. The rationale for not reducing the dose at the time of this review in 2007 was because doses of 500 mg were safely being administered in ongoing clinical trials. However, since the current submission introduces a new dosing regimen (500 mg + AD) and doses greater than 500 mg have not been tested in humans, the safety profile of the 500 mg + AD regimen is uncertain in patients with moderate hepatic impairment. Therefore, a 250 mg dose is recommended for patients with moderate hepatic impairment.

1.1 RECOMMENDATIONS

This application is acceptable from a clinical pharmacology perspective, provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

Labeling Recommendations

The Clinical Pharmacology sections of the labeling for FASLODEX™ have been reproduced within the Detailed Labeling Recommendations Section below.

Signatures:

Reviewer: Young Jin Moon, Ph.D. Division of Clinical Pharmacology 5	Team Leader: Julie Bullock, Pharm.D. Division of Clinical Pharmacology 5

Cc: DDOP: CSO - A Davis-Warren ; MTL - A Ibrahim; MO - T Prowell
DCP-5: Reviewer - Y Moon, N Mehrotra; TL-J Bullock, C Garnett;
DDD - B Booth; DD - A Rahman

1.2 CLINICAL PHARMACOLOGY SUMMARY

FASLODEX (fulvestrant) is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner with affinity comparable to that of estradiol. FASLODEX was approved on 4/25/02 for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy (Original NDA 21-344, Submission Date: 3/28/01). The approved dose of 250 mg is administered intramuscularly (IM) once a month as either a single 5 mL injection or two concurrent 2.5 mL injections. (b) (4)

The current submission provides safety and efficacy information to support a dose change from the currently approved 250 mg dose to a 500 mg monthly IM dose with an additional dose (AD) given two weeks after the initial dose. Two supporting phase 2 trials (FINDER 1 and FINDER 2) assessed the PK of fulvestrant after administration of the following regimens:

- 250 mg: 250 mg at intervals of one month
- 250 mg + AD: 500 mg on Day 1; 250 mg on Days 15, 29, and monthly thereafter
- 500 mg + AD: 500 mg on Days 1, 15, 29 and monthly thereafter

Both studies were randomized, double-blind, parallel-group, multicentre studies in postmenopausal Japanese (FINDER 1) and Caucasian (FINDER 2) women with estrogen receptor positive advanced breast cancer.

The sparse data from FINDER 1 and 2 were analyzed using a non-linear mixed effects approach. A two-compartment model with a first order absorption and first order elimination process was fitted to the combined data. CL/F was estimated at a mean of 30.7 L/hr (CV 36.2%). The mean estimate of Vss/F (V1/F + V2/F) was 56100 L (V1/F, CV 37.8%). The pharmacokinetics of fulvestrant appear to be similar in Caucasian and Japanese patients as previously reported in the original submission. The additional 500 mg dose of FASLODEX given on Day 15 after initial dose on Day 1 causes plasma levels to reach close to steady state within first month of dosing. The pharmacokinetics of fulvestrant appeared to be linear across the dosing regimens studied.

2 QUESTION BASED REVIEW

Refer to the original NDA 21-344 (Approval Date: 4/25/02) for additional clinical pharmacology details.

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

2.1.3 What are the proposed dosage and route of administration?

The applicant proposed a dose change from the currently approved 250 mg monthly dose. The proposed dose for this supplement is a 500 mg IM injection at intervals of one month with an additional 500 mg dose given two weeks (on Day 15) after the initial dose.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The applicant conducted 5 clinical studies (Table 1).

Table 1 Clinical studies

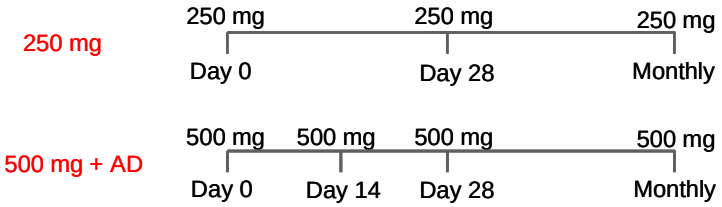
Study	Study design	Objectives (primary)	Dose Regimens [a] (number of patients)
Pivotal phase III study pertinent to the proposed dose regimen and indication			
CONFIRM (D6997C00002)	Randomized, double blind, parallel group, multicenter	Efficacy (PFS) and safety	500 mg + AD (362) 250 mg (374)
Phase II studies pertinent to the proposed dose regimen and indication			
FINDER1 (D6997C00004)	Randomized, double blind, parallel group, Multicenter in Japan	Efficacy (ORR), PK and safety	500 mg + AD (47) 250 mg (45) 250 mg + AD (51)
FINDER2 (D6997C00006)	Randomized, double blind, parallel group, Multicenter In Western Countries	Efficacy (ORR), PK and safety	500 mg + AD (46) 250 mg (47) 250 mg + AD (51)
Other phase II studies not directly relevant to the evaluation of efficacy in the proposed indication			
NEWEST (D6997C00003)	Randomized, open label, multicenter	Efficacy (Ki67 LI), PK, PD and safety	500 mg + AD (109) 250 mg (102)
FIRST (D6995C00006)	Randomized, open label, parallel group, multicenter	Efficacy (CBR) and safety	500 mg + AD (102) Anastrozole 1 mg (103)

a 250 mg: 250 mg at intervals of one month
250 mg + AD: 500 mg on Day 1; 250 mg on Days 15, 29, and monthly thereafter
500 mg + AD: 500 mg on Days 1, 15, 29 and monthly thereafter

Pivotal Study

The pivotal phase 3 study D6997C0002 (CONFIRM) was conducted in 736 postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. This trial

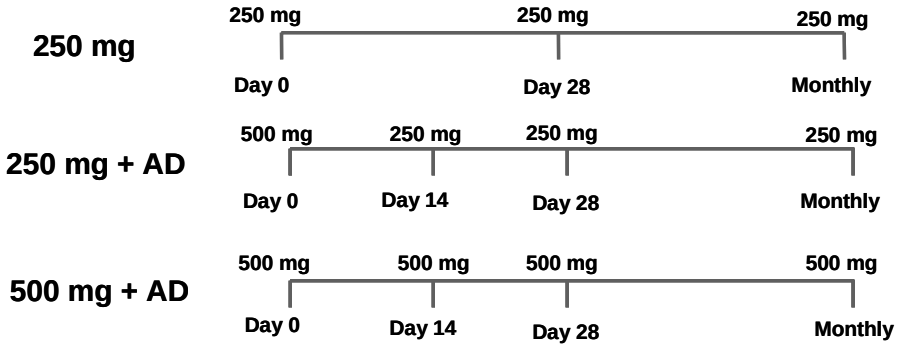
compared the efficacy and safety of fulvestrant 500 mg with additional dose (AD) (n=362) with fulvestrant 250 mg (n=374). The primary efficacy endpoint was progression free survival (PFS).



The median PFS was 6.5 months in the 500 mg FASLODEX with additional dose group and 5.4 months in the 250 mg FASLODEX group (hazard ratio 0.8, 95% CI: 0.68-0.94, p = 0.006).

Clinical Pharmacology Studies

Overall Response rate was the primary endpoint for the phase 2 studies D6997C0004 (FINDER1) and D6997C0006 (FINDER2) in 143 Japanese patients and 144 Caucasian patients with estrogen receptor positive advanced breast cancer progressing or relapsing after previous endocrine therapy. These studies also assessed the PK of fulvestrant in patients treated with varying fulvestrant regimens outlined in the figure below:



2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Biomarkers

Study NEWEST (D6997C00003) compared the effects of fulvestrant 500 mg + AD and 250 mg on the proliferation marker Ki67 after 4 weeks of treatment and assessed the PD markers of down-regulation and proliferation and the correlation between changes in Ki67 labeling index and changes in ER expression and progesterone-receptor (PgR) expression.

Ki67 is expressed in all phases of mitosis (G1 through S) and thus is used as a marker of cell proliferation, i.e., tumor growth. Immunostaining of Ki67 in paraffin-embedded or frozen tumor samples provides a basis for quantification, with percent of stained cells incorporated into a proliferation index.

ER and PgR Intensity Scores were analyzed using a (b) (4) . The (b) (4) uses computer assisted digital imaging to detect and count individual pixels of a chromogen color (brown = positive; blue = negative) and calculates the percentage of nuclei that are positively stained and the mean intensity of the stain.

Clinical Endpoints
The clinical endpoints of FASLODEX are shown above in Table 1. The pivotal efficacy trial used PFS as the primary endpoint. PFS was defined as the time from randomization to the time of the earliest evidence of objective disease progression or death from any cause prior to documented progression. Death was regarded as a progression event in those patients who died without evidence of disease progression.

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single dose and multiple dose PK parameters?

The PK of fulvestrant 500 mg + AD was characterized in two phase 2 studies FINDER1 and FINDER2 using population PK analysis. Both studies were randomized, double-blind, parallel-group, multicentre studies in postmenopausal Japanese (FINDER1) and Caucasian (FINDER2) women with estrogen receptor positive advanced breast cancer.

Sparse PK samples were collected from 36 patients (how many in each study?). Samples were taken at Day 1, Day 15, Day 29, Day 57 and Day 85 just prior to the randomized treatment injections. Two additional samples were also taken at any time between Day 6 - 11 and between Day 34 – 39. The PK parameters for the 500 mg + AD were derived from modified model by the reviewer (Table 2).

Table 2: Summary of fulvestrant pharmacokinetic parameters (Mean ± SD) in postmenopausal advanced breast cancer patients after intramuscular administration of a 500 mg + AD dosing regimen (N=36)

		C_{max} (ng/mL)	**C_{min} (ng/mL)**	**AUC (ng.d/mL)**
500 mg + AD*	Single dose	26.5 ± 8.3	16.8 ± 4.0	497 ± 148
	Multiple dose steady state**	28.8 ± 7.7	12.5 ± 2.7	556 ± 128

* additional 500 mg dose given on day 15

** month 3

2.2.5.9 How do the PK parameters change with time following chronic dosing?

An additional dose at Day 15 causes plasma levels to reach close to steady state within the first month of dosing. The mean plasma concentration profiles for a 70 kg patient after 500 mg + AD (proposed dose) and 500 mg without AD were predicted based on the parameter estimates obtained from the population pharmacokinetic model (Figure 1; refer to Section 4. Pharmacometrics Review). Eventually similar steady state levels will be achieved with these two dosing regimens. However, for the first two months, the 500 mg + AD regimen results in higher exposures (close to steady state exposures) compared to 500 mg without AD regimen.

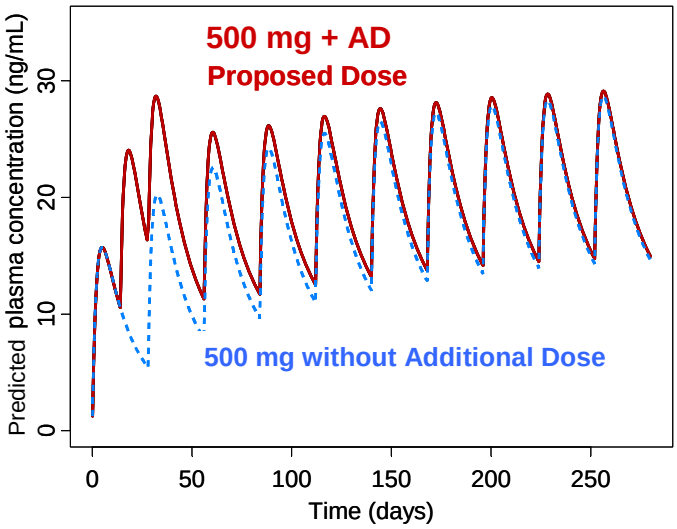


Figure 1. The predicted mean plasma concentration profiles for a 70 kg individual after 500 mg + AD (solid red line) and 500 mg without AD (dotted blue line) were administered.

The above result was also expressed by % of steady state reached at each cycle (Figure 2). Using the average half life of 40 days, steady state would be reached at cycle 9. Percent of steady state reached was calculated from trough concentrations at each cycle divided by trough concentrations at cycle 9. It can be seen that the additional dose at Day 15 causes concentrations close to steady state levels within one month of dosing.

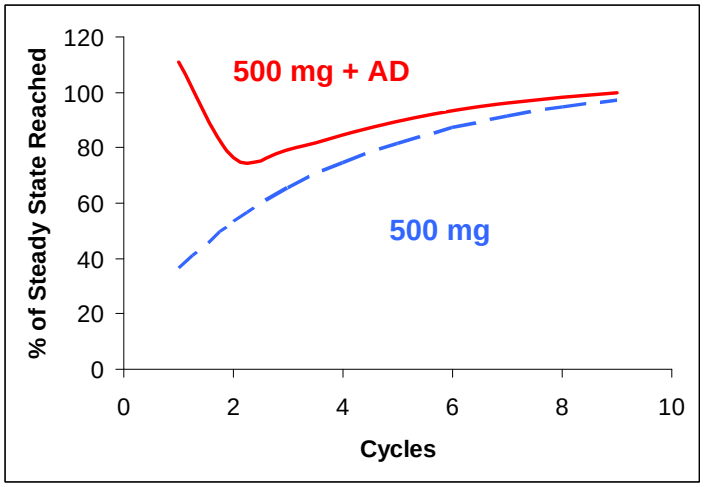


Figure 2. % of steady state at each cycle

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Based on population PK analysis (Table 3), inter-individual variability of CL and V was 36.2% and 37.8%, respectively. Residual error was 22.4%. Please see the population PK analysis in Section 4 for more details.

Table 3. Population PK parameters

	Mean
Ka (h^{-1})	0.02 (fixed)
CL/F (L/hr)	30.7
V1/F (L)	20400
Q (L/hr)	29.6
V2/F (L)	35700
V1WT	1
CLWT	0.49
IIV* (CL/F)	36.2
IIV (V1/F)	37.8
Corr** (CL/F-V/F)	96.4
Residual error (CV%)	22.4

*IIV, inter-individual variability
**Corr, Correlation coefficient

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Population PK analysis

The oral clearance and volume of distribution did not depend on age, BMI, IBW, dose or race. Differences between population and individual predicted clearance from the final population PK model were compared between Japanese and Caucasian patients (Figure 3). There was no difference in clearance between Japanese and Caucasian patients.

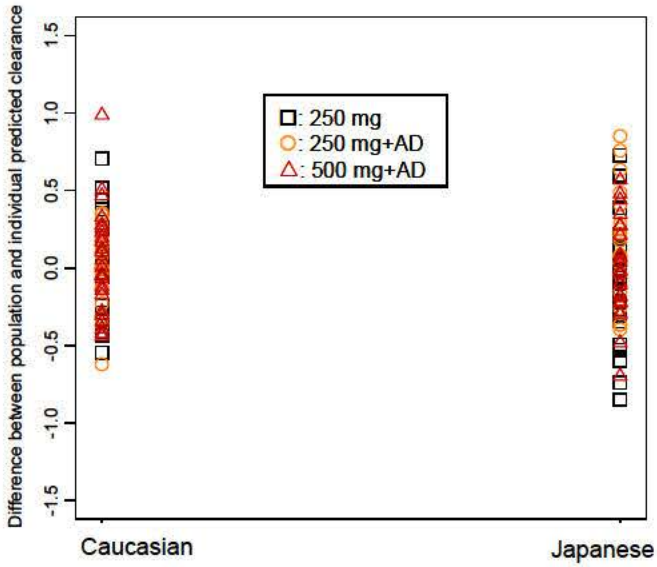


Figure 3. Difference between population and individual predicted clearance were similar in Caucasian and Japanese patients.

Observed data

There was no significant difference in observed trough concentration between Japanese and Caucasian patients following three different doses at Month 3 (Figure 4)

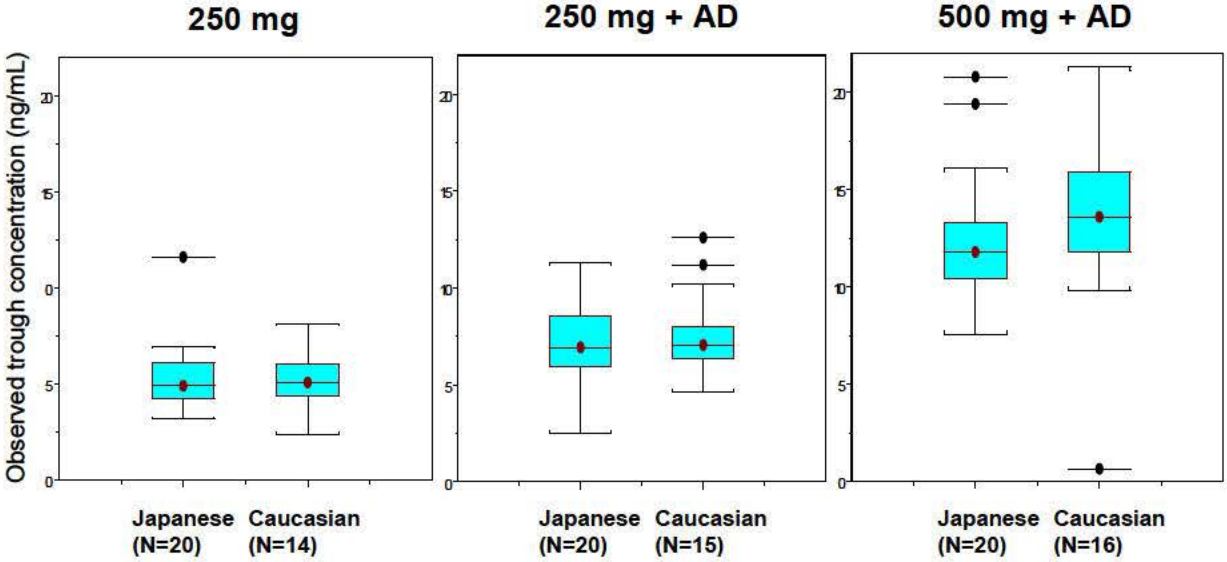


Figure 4. Observed trough concentrations (ng/mL) in Japanese and Caucasian patients at 250 mg, 250 mg + additional dose (AD) and 500 mg + AD.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.3 Hepatic impairment

The sponsor conducted a dedicated study (Study 0063) to assess the effect of hepatic impairment on plasma exposure of fulvestrant (21-344/SLR-007; Submission Date 12/01/05). This study was reviewed by Dr. Sophia Abraham (DARRTS communication date 2/26/07) and is summarized below.

Study 0063 was a single-dose, open-label, parallel-group study in two hepatically impaired groups of seven (7) subjects each (Child-Pugh A and B) and a control group of seven (7) healthy subjects with normal hepatic function. Each subject received a single 100 mg dose of fulvestrant via the intramuscular route. The short acting (SA) formulation used in this study is different from the marketed long acting (LA) formulation. The results of this study demonstrate that subjects with moderate hepatic impairment (Child-Pugh B) had about 1.7-fold higher exposure (mean AUC) to fulvestrant than those with normal hepatic function. The relationship between AUC and total bilirubin was significant (p=0.012). Subjects with mild hepatic impairment (Child-Pugh A) had comparable exposure to fulvestrant to those with normal hepatic function.

Table 4. Statistical Analysis of $AUC_{0\text{-}96}$ and C_{max} of Fulvestrant – Child-Pugh A (Mild) Group versus control subjects (taken from Dr. Sophia Abraham's review)

	Controls (Glsmean*)	Child-Pugh A (Glsmean*)	Estimate ratio (Child-Pugh A /Controls)	90% CI
$AUC_{0\text{-}96h}$ (ng.h/ml)	1436	1762	1.23	79-189%
C_{max} (ng/ml)	36.25	51.1	1.41	65-304%

* Geometric least squares mean CI=Confidence Interval

Table 5. Statistical Analysis of $AUC_{0\text{-}96}$ and C_{max} of Fulvestrant – Child-Pugh B (Moderate) Group versus control subjects (taken from Dr. Sophia Abraham's review)

	Controls (Glsmean*)	Child-Pugh B (Glsmean*)	Estimate ratio (Child-Pugh B /Controls)	90% CI
$AUC_{0\text{-}96h}$ (ng.h/ml)	1436	2514	1.75	115-267%
C_{max} (ng/ml)	36.25	54.25	1.49	83-270%

* Geometric least squares mean CI=Confidence Interval

Dr. Abraham concluded that the normal adult dose of 2.5-mL (250 mg) IM of the LA formulation given once a month could be also administered to the patients with moderate hepatic impairment (Child-Pugh B) based on the following facts:

- No major toxicities were observed in the study in patients with moderate hepatic impairment.
- The lower dose (i.e., 125 mg) did not show promising efficacy (Original NDA).
- In general, the toxicities were mild (e.g., anti-estrogenic type: hot flashes, myalgias) after using the marketed long acting (LA) formulation in breast cancer patients. The spectrum of toxicities seen so far does not include life threatening toxicities.
- Twice the approved dose of 250 mg (i.e. 500 mg), is being administered in some ongoing trials, and is tolerated. Treated patients, so far, have been the ones with metastatic disease and they do not live long enough to manifest long term toxicities from estrogen deprivation (e.g. osteoporosis).

Reviewer's Comment: Since doses higher than 500 mg have not been tested, the safety profile of a 500 mg dose is uncertain in patients with moderate hepatic impairment given the exposure increases seen in the hepatic impairment trial. Therefore, a 250 mg dose is recommended for patients with moderate hepatic impairment.

3 DETAILED LABELING RECOMMENDATIONS

Labeling recommendations are being communicated directly to the review team. The major recommendation is as follows:

A 250 mg dose with additional dose on Day 15 should be used in patients with moderate hepatic impairment.

4 PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Application Number	21-344 SE12
Submission Number (Date)	November 12, 2009
Clinical Division	DDOP
Primary PM Reviewer	Young Jin Moon, Ph.D.
Secondary PM Reviewer	Nitin Mehrotra, Ph.D.
PM Team Leader	Christine Garnett, Pharm.D.

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The following key questions were addressed in this pharmacometric review.

1.1.1 Does the 500 mg + additional dose (AD) achieve exposure levels close to the steady state concentrations within the first month of dosing?

Yes, an additional dose at Day 15 causes plasma levels to reach steady state concentrations within the first month of dosing. The mean plasma concentration profiles for a 70-kg patient after 500 mg + AD (proposed dose) and 500 mg without AD were predicted based on the parameter estimates obtained from the population pharmacokinetic model (Figure 1).

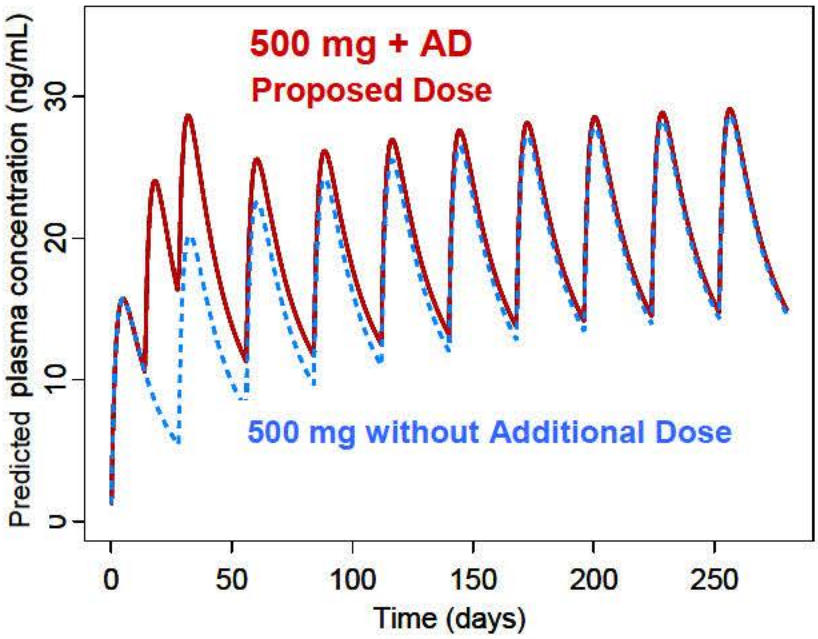


Figure 1. The predicted mean plasma concentration profiles for a 70-kg individual after 500 mg + AD (solid red line) and 500 mg without AD (dotted blue line).

The above result was also expressed by % of steady state reached at each cycle (Figure 2). Based on the half life of fulvestrant (~40 days), steady state would be reached at cycle 9. Percent of steady state reached was calculated by trough concentration at each cycle divided by trough concentration at cycle 9. It can be seen that an additional dose at Day 15 causes concentrations close to steady state levels within one month of dosing.

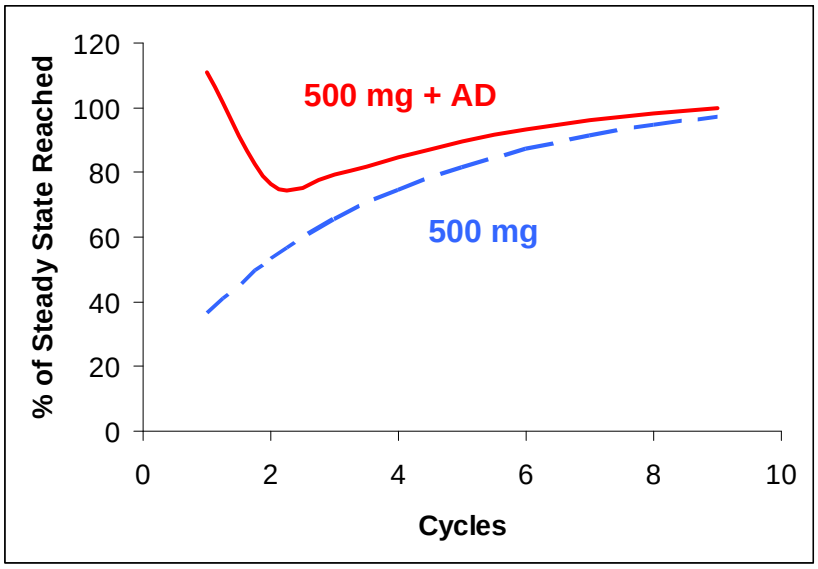


Figure 2. % of steady state reached at each cycle

1.1.2 Is there a difference in PK between Japanese and Caucasian patients?

No, there was no significant difference in observed trough concentration between Japanese and Caucasian patients following three different doses at Month 3 (Figure 3).

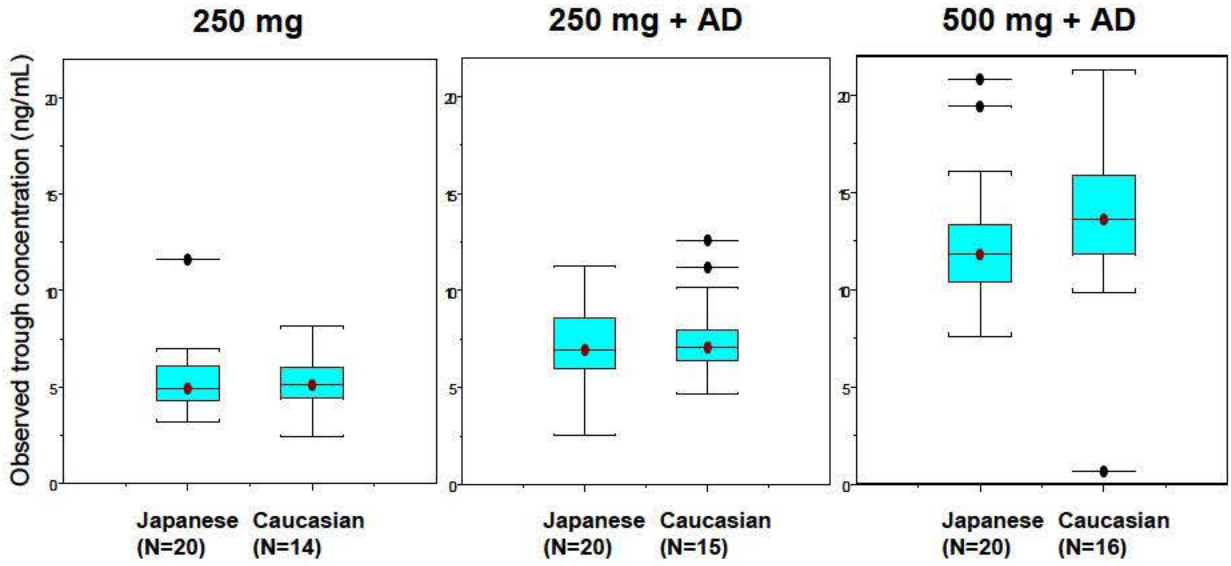


Figure 3. Observed trough concentrations (ng/mL) in Japanese and Caucasian patients at 250 mg, 250 mg + additional dose (AD) and 500 mg + AD.

Also, differences between population and individual predicted clearance from the final population PK model were compared between Japanese and Caucasian patients (Figure 4). Clearance values were similar between two groups regardless of dose levels.

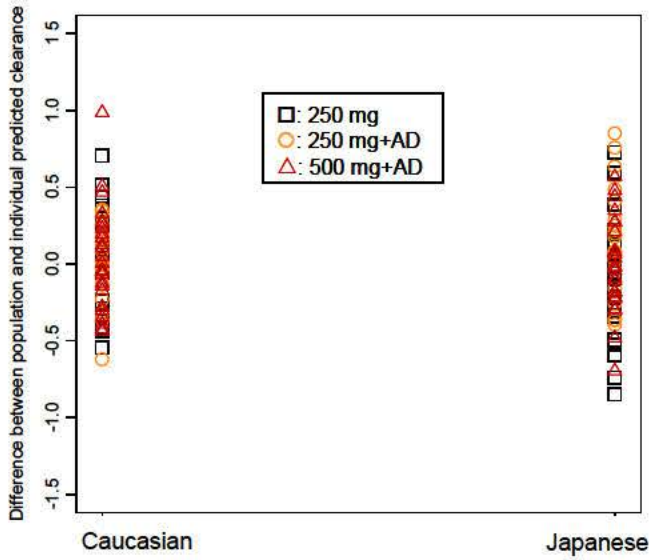


Figure 4. Difference between population and individual predicted clearance were similar in Caucasian and Japanese Patients.

Therefore, the difference in median progression free survival (PFS) between Japanese and Caucasian patients (Table 1) shown in the 250-mg dose group cannot be explained by PK. For other two dosing regimens median PFS were similar.

Table 1. Summary of median PFS in phase 2 studies FINDER1 and FINDER2

	250 mg	250 mg +AD	500 mg + AD
Caucasian (FINDER2)	3.1 (N=47)	6.1 (N=51)	6.0 (N=46)
Japanese (FINDER1)	6.0 (N=45)	7.5 (N=51)	6.0 (N=47)

When Faslodex was initially approved in 2002, the registration trial included mainly Caucasian patients (Caucasian 349, Black 2, other 9), median PFS at 250 mg (N=374) was 5.4 month which is close to 6.0 month. Therefore, the lower PFS observed in 250 mg Caucasian patients group (Table 1) may be due to the small number of patients.

1.2 Recommendations

The current submission is acceptable from a clinical pharmacology perspective.

1.3 Label Statements

Please refer to Section 3, Detailed Labeling Recommendations in Clinical Pharmacology Review.

2 RESULTS OF SPONSOR'S ANALYSES

The key findings from sponsor's analyses are summarized and discussed below.

2.1 Population Pharmacokinetic Analysis of fulvestrant

A population model describing the PK of fulvestrant was already developed using data from Studies 9238IL/0020 and 9238IL/0021 (pivotal studies of original NDA). In the current submission, the same model was updated using the PK data from a total of 142 patients (788 observations), which was available from two Phase 2 studies. Description of the studies with other relevant information is provided in Table 2.

Table 2. Study characteristics

Study No.	Sample size	Nominal doses studied (mg/m^2)	Indication	Sample collection
9238IL/0066	70	250 mg, 250 mg + AD, 500 mg + AD, monthly	ER+ Advanced Breast Cancer	Sparse
8238IL/0068	72	250 mg, 250 mg + AD, 500 mg + AD, monthly	ER+ Advanced Breast Cancer	Sparse

The key findings from sponsor's population PK analysis are summarized below:

- A two-compartment model with a first order absorption and first order elimination process was fitted to the fulvestrant concentration-time data:
    - CL/F was estimated at a mean of 31.0 L/hr (CV 39%). The mean estimate of Vss/F (V_1/F + V2/F) was 56300 L (V_1/F, CV 40%).
    - No relationship was identified between ethnicity and either CL/F or V_1/F. Individual estimates of V_1/F were found to be significantly positively correlated to body weight.
    - CL/F and V_1/F were found to be positively correlated (correlation coefficient 0.964). Residual variability was proportional in nature (CV 22%) and parameters were generally well estimated (relative standard error (RSE) < 17% except for V2/F (RSE 28%)).
- Secondary parameters are detailed in Table 3 below:

Table 3. Secondary pharmacokinetic parameter estimates for month 1 and 3

	250 mg	250 mg loaded	500 mg loaded
t ½ (mean, SD)	58.5 (±14.6) days	52.5 (±10.2) days	54.3 (±10.4) days
R_{ac} [b] (median, range)	3.38 (2.34-5.81)	NA	NA
n	47	45	50
	Month 1 (Visit 4)		
C_{max} [c] (gmean, CV)	9.12 ng/mL (46.4%)	16.1 (25.2%)	25.1 ng/mL (35.3%)
t_{max} [d] (median, min-max)	4.7 days (3.7-5.9 days)	3.6 days (3.2-4.0 days)	4.1 days (3.5-4.9 days)
C_{min} (gmean, CV)	2.76 ng/mL (20.1%)	10.3 ng/mL (18.7%)	16.3 ng/mL (25.9%)
$AUC_{(0-\tau)}$ (gmean, CV)	3720 ng.hr/mL (35.6%)	8800 ng.hr/mL (25.3%)	11400 ng.hr/mL (33.4%)
n	47	42 [e]	49 [f]
	Month 3 (Visit 7)		
C_{max} (gmean, CV)	13.8 ng/mL (34.3%)	14.1 (26.7%)	28.0 (27.9%)
t_{max} (median, min-max)	4.4 days (3.6-4.8 days)	4.3 days (3.9-4.6 days)	4.3 days (3.9-4.7 days)
C_{min} (gmean, CV)	5.39 ng/mL (24.5%)	6.50 ng/mL (26.4%)	12.2 ng/mL (21.7%)
$AUC_{(0-\tau)}$ (gmean, CV)	6130 ng.hr/mL (27.8%)	6780 ng.hr/mL (25.0%)	13100 ng.hr/mL (23.4%)
n	34 [g]	35 [e]	36 [f]

[a] Derived from raw data
[b] R_{ac}, accumulation ratio
[c] C_{max}, the highest concentration between days 0 and 28 (dose on day 14 for 250 mg LD and 500 mg)
[d] t_{max}, the elapsed time between dosing and the maximum concentration up to 28 days
[e] 1 subject was dosed up to day 0, 2 patients were dosed up to day 14, 1 subject was dosed up to day 28 & 6 patients were dosed up to day 56 (n=10)
[f] 1 subject was dosed up to day 14, 3 patients were dosed up to day 28 & 10 patients were dosed up to day 56 (n=14)
[g] 1 subject was dosed up to day 28 & 12 patients were dosed up to day 56 (n=13)

Source: Table 7, The applicant's population analysis report on Page 15

Reviewer's comments on the sponsor's population PK analysis:

1) *Reviewer evaluated the possibility of including weight as a covariate on clearance which is consistent with the elimination mechanism (hepatic) of fulvestrant. By adding WT into CL, objective function was reduced by 18.2 from the sponsor's final model (See Section 3. Reviewer's Analysis for details). Although the model was slightly changed by reviewer, the population parameter estimates were similar.*
2) *There was discrepancy in the standard errors of estimated parameters generated by the applicant and by reviewer. Especially the reviewer's RSEs obtained by using the sponsor's 'Model 0' were higher than the sponsor's RSEs.*
3) *Although V2/F value was fixed, standard error value for V2 was reported in Table 5 (page 12) of the sponsor's report.*

3 REVIEWER'S ANALYSIS

The identified issues in sponsor's analysis are addressed in the following.

3.1 Population Pharmacokinetic Analysis of Faslodex

3.1.1 Objectives

The reviewer's analysis objectives are:

1) To evaluate the sponsor's population PK model.
2) To verify the proposed labeling statements describing the PK parameters.
3) To investigate if there is a difference in PK between Japanese and Caucasian patients.

3.1.2 Methods

Two phase 2 trials D6997C0004 (FINDER1) and D6997C0006 (FINDER2) were conducted in 143 Japanese patients and 144 Caucasian patients with estrogen receptor positive advanced breast cancer progressing or relapsing after previous endocrine therapy. These studies assessed the PK of fulvestrant in patients treated with fulvestrant 250 mg, 250 mg + AD regimen and 500 mg + AD. Data from these two supporting trials were used for the population pharmacokinetic analysis of Faslodex. No PK data was collected in the phase 3 pivotal trial,

Non-linear mixed effect modeling was used to describe the data and FOCE method with interaction was utilized to develop covariate models. The final model was used to simulate mean population profiles for a 70 kg individual at the different dosing regimens, and the steady state PK profiles were predicted.

Efficacy endpoint of these phase 2 trials was median PFS. The analysis of PFS is summarized in Table 1. The median for PFS in the fulvestrant 250 mg in Japanese patients was numerically longer than the median PFS of fulvestrant 250 mg in Caucasian patients. To answer whether the lower efficacy can be linked to lower exposure, PK in Japanese and Caucasian patients were compared.

3.1.2.1 Data Sets

Data sets used are summarized in Table 4.

Table 4: Analysis Data Sets

Study Number	Name	Link to EDR
FINDER1 and FINDER 2	combined-f1f2appb.xpt combined-f1f2appc.xpt	\NDA021344\0011\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\combined-pop-pk\crt\datasets

3.1.2.2 Software

(b) (4) was used to review the sponsor's population PK analysis. (b) (4) was used to generate all plots and manage datasets.

3.1.3 Models

In the applicant's analysis weight was not incorporated as a covariate for CL. Since Faslodex is eliminated by liver, weight should likely be a covariate on clearance. Nine codes (Table 5) were run using the 2-compartment structural model to see the plausibility of including weight on clearance.

Table 5. Model description

	model 1	no omega block (2)
Sponsor's Base	model 2	Omega block included but no covariate
	model 3	WT on CL (power coefficient fixed to 0.75)
	model 4	WT on CL (power coefficient estimated)
	model 5	WT on V (power coefficient fixed to 1)
Sponsor's Final	model 6	WT on V (power coefficient estimated)
Reviewer's Final	model 7	WT on CL and V (both power coefficients estimated)
	model 8	WT on CL and V, V2WT=1 (fixed), CLWT estimated
	model 9	Both power coefficient fixed

3.1.4 Results

Review of Model Selection

Following the visual inspection (Figure 5 Base model), weight (WT) was introduced into both CL (CL=TVCL*(WT/61)$^{\theta}$) and V (V=TVV*(WT/61)$^{\theta}$).

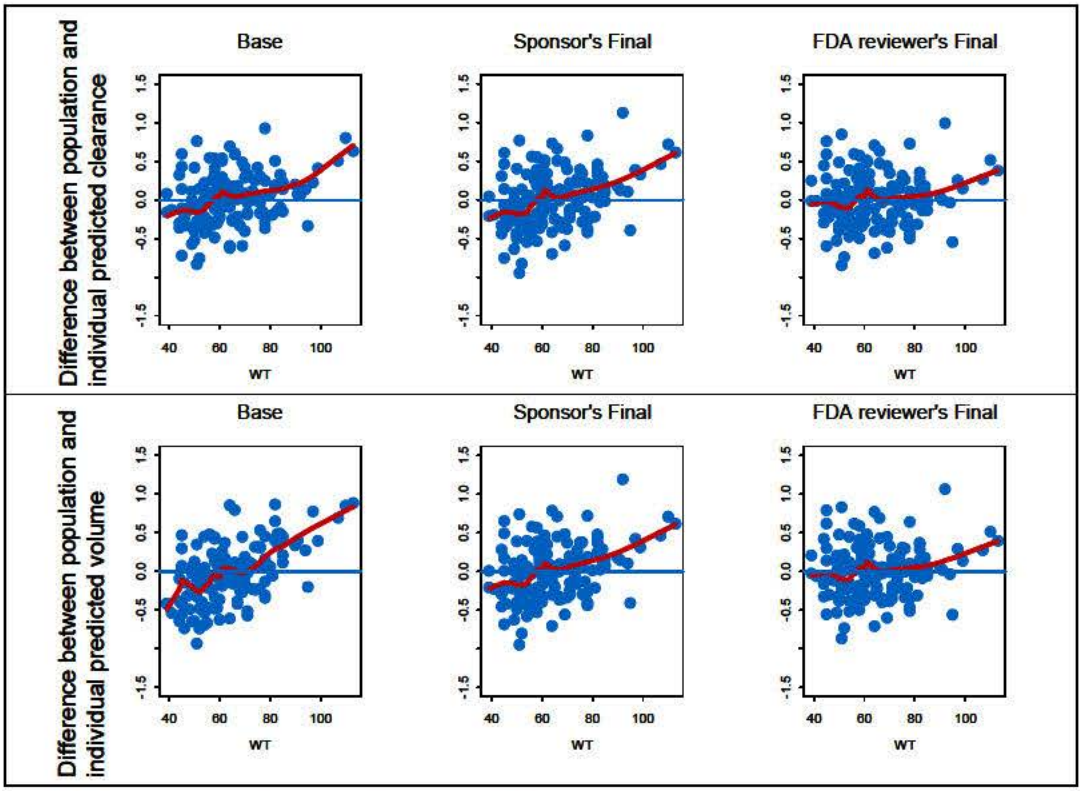


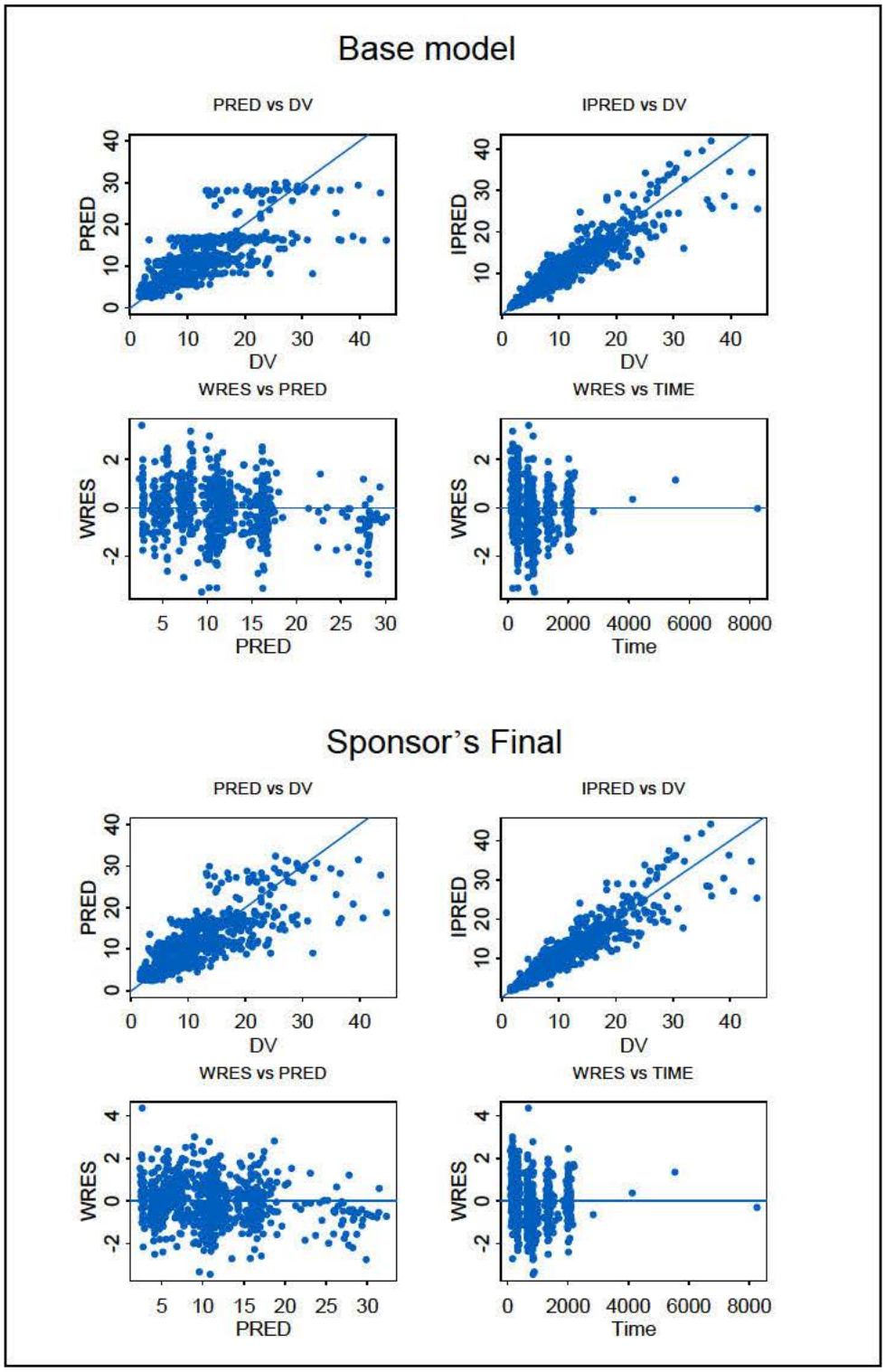
Figure 5. Covariates plot for CL (ETA1) and V (ETA2) using base model, the sponsor's final model (Model 6) and the reviewer's final model (Model 7).

Population PK parameters using base model, the sponsor's final model, and the reviewer's final model were compared in Table 6.

Table 6. Population PK parameters

	model 1	model 2	model 3	model 4	model 5	model 6 (sponsor's final)	model 7 (reviewer's final)	model 8	model 9
	mean	mean	mean	mean	mean	mean	mean	mean	mean
Ka	0.02 (fixed)	0.02 (fixed)	0.02 (fixed)	0.02 (fixed)	0.02 (fixed)	0.02 (fixed)	0.02 (fixed)	0.02 (fixed)	0.02 (fixed)
CL/F	30.1	31.2	30	31.2	30.7	31	30.7	30.7	30.5
V1/F	21200	20800	20700	20800	20400	20600	20400	20300	20300
Q	31.3	30.1	31.3	30.1	29.9	29.7	29.6	29.6	29.9
V2/F	35700	35700	35700	35700	35700	35700	35700	35700	35700
V2WT	None	None	None	None	1 (fixed)	0.7	1	1 (fixed)	1 (fixed)
CLWT	None	None	0.75 (fixed)	4.22E-08	None	None	0.49	0.49	0.75 (fixed)
IIV (CL/F)	37.1	39.2	36.7	39.2	38.3	38.7	36.2	36.2	36.5
IIV (V1/F)	47.6	47	47.4	47	38.2	39.6	37.8	37.8	37.7
Corr (CL/F-V/F)	None	94.9	75.2	94.9	93.5	96.4	96.4	96.4	94.6
Residual error	22.7	22.6	22.6	22.6	22.4	22.4	22.4	22.4	22.4
MOF	-1072.03	-1202.056	-1145.86	-1202.056	-1229.228	-1235.056	-1253.28	-1253.283	-1245.85
△OF		130.026	73.83	130.026	157.198	163.026	181.253	181.253	173.824

Goodness of fit plots were also compared (Figure 6).


Base model
PRED vs DV
PRED
DV
IPRED vs DV
IPRED
DV
WRES vs PRED
WRES
PRED
WRES vs TIME
WRES
Time
Sponsor's Final
PRED vs DV
PRED
DV
IPRED vs DV
IPRED
DV
WRES vs PRED
WRES
PRED
WRES vs TIME
WRES
Time

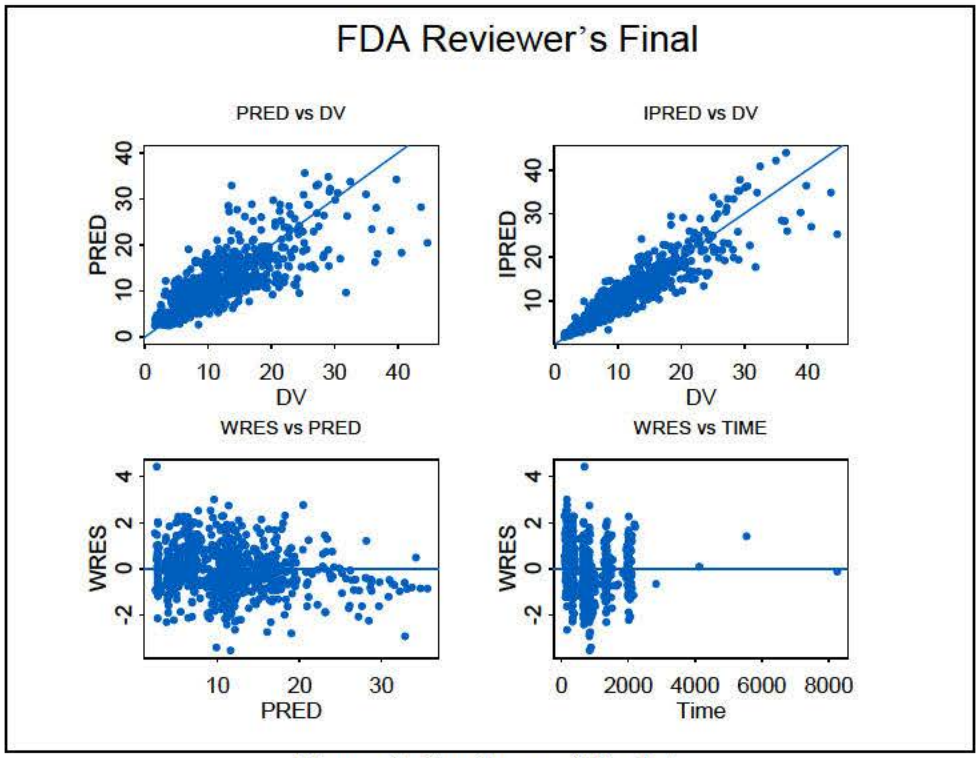


Figure 6. Goodness of fit plots

By adding weight as a covariate on CL, objective function was reduced by 18.2 from the sponsor's final model and inter-individual variability of CL was also decreased from 38.7 to 36.2% (Table 6). DV-PRED plot also showed some improvement Figure 6). Although the model was slightly changed by reviewer, the population parameter estimates were similar.

Figure 7 shows the relationship of clearance and volume with weight with mean population predictions overlaid with the individual level data, depicting that model reasonably described the data.

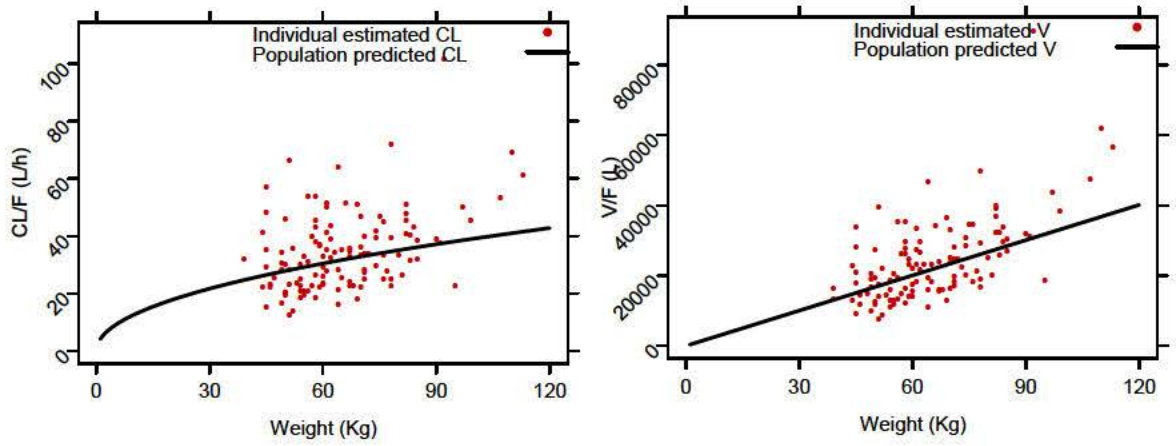


Figure 7. Effect of weight on fulvestrant clearance (left) and volume of distribution (right) over the observed range of weight

On August 12, 2010, teleconference with the sponsor was held and discussed on PK parameter values (AUC, C_{max} and C_{min}) reported in Table 3 in the labeling which were different from the values proposed by the sponsor. FDA stated that the population PK model was modified by the FDA reviewer to include weight on both clearance and volume of distribution as apposed to weight only on volume of distribution proposed by sponsor. Since the PK parameters were similar (< 5% difference) between Sponsor's and FDA Reviewer's model, FDA would accept PK parameters originally proposed by the sponsor.

Simulation

The mean simulated predicted plasma concentration profiles for a 60 kg patient after a 250 mg, 250 mg + AD and 500 mg + AD dosing regimen are shown in Figure 8.

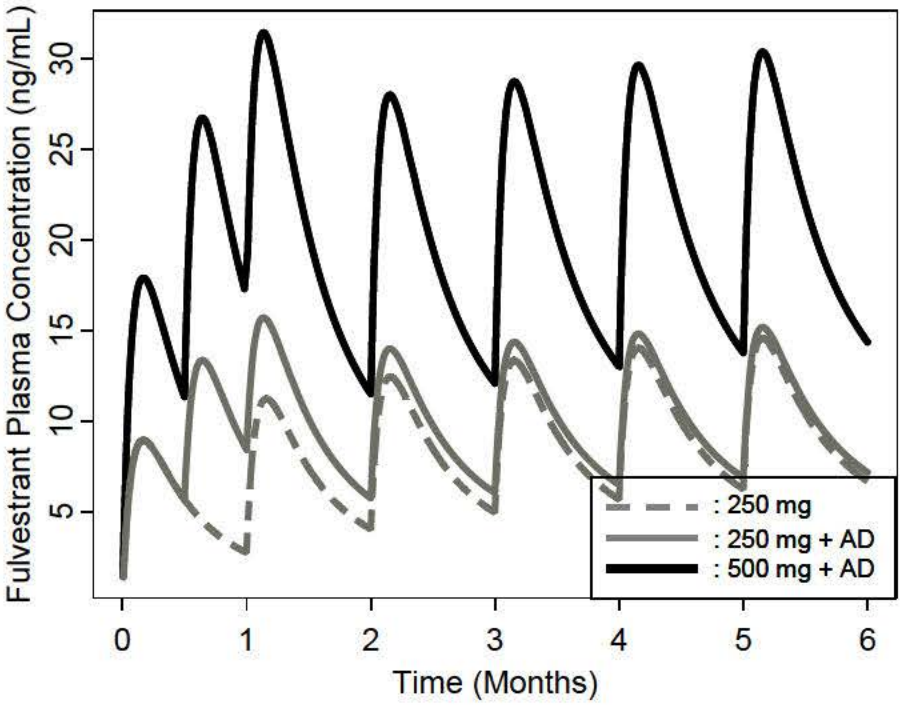


Figure 8. The predicted mean plasma concentration profiles for a 60 kg patient after 250 mg (dotted gray line), 250 mg + AD (solid gray line), 500 mg + AD (solid black line) dosing regimen.

Although 250 mg + AD dosing regimen was not tested, it is included in the label for patients with moderate hepatic impairment, as it is expected to allow for steady state concentrations to be reached within the first month of dosing (Figure 8).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

YOUNG J MOON
08/18/2010

NITIN MEHROTRA
08/18/2010

CHRISTINE E GARNETT
08/18/2010

JULIE M BULLOCK
08/18/2010

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

NDA Number	21-344	**Brand Name**	FASLODEX™
DCP Division	5	**Generic Name**	Fulvestrant
Medical Division	Oncology	**Drug Class**	Estrogen Receptor Antagonist
OCP Reviewer	Young-Jin Moon	**Indication(s)**	For the treatment of hormone receptor positive metastastic breast cancer in postmenopausal women with disease progression following antiestrogen therapy
OCP Team Leader	Brian P Booth	**Dosage Form**	An injection for intramuscular administration, supplied as 50 mg/mL fulvestrant
Date of Submission	November 12, 2009	**Dosing Regimen**	500 mg to be administered as two 5 mL injections, one in each buttock, at intervals of one month with an additional 500 mg dose given two weeks after the initial dose
Due Date of OCP Review		**Route of Administration**	Intramuscular administration
Standard PDUFA Due Date	September 13, 2010	**Sponsor**	AstraZeneca

Clinical Pharmacology Information

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

Subpopulation studies -				
ethnicity:				
gender:				
geriatrics:				
renal impairment:				
hepatic impairment:				
pediatrics:				
PD:				
Phase 2:		**3**		
Phase 3:		**1**		
PK/PD:				
Phase 1 and/or 2, proof of concept:	**X**	**1**		Population PK analysis report and NONMEM dataset could not be found.
Phase 3 clinical trial:				
Population Analyses -				
Data rich:		**3**		From two phase 2 studies and one PK/PD study,
Data sparse:	**X**			Only one population PK study report is found. NONMEM dataset should be in SAS file.
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
QTC studies:				
In-Vitro Release BE				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Biliary Elimination				
Pediatric development plan				
Literature References				
Total Number of Studies		**5**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction			X	

	information?				
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?		X		NONMEM dataset should be submitted in SAS format.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			

19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Clinical Pharmacology Comments

Population PK analysis reports for studies D6997C00006 and D6997C00003, as well as combined analysis (D6997C00004 and D6997C00006) could not be found in your submission. Please submit these population PK analysis reports.

Also, please submit the following datasets /control streams to support all the above mentioned population PK analysis reports (including your stand alone population PK study for D6997C00004):

- All NONMEM datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

Young-Jin Moon 12/14/2009

Reviewing Clinical Pharmacologist Date

Brian P Booth 12/14/2009

Deputy Division Director Date

CC: **DDOP: (CSO –** A Davis-Warren; **MTL –** A Ibrahim; **MO –** T Prowell**)**
DCP5: (Reviewer - Y Moon; N Mehrotra; PM TL – C Tornoe; **DDD -** B Booth; **DD -** A Rahman**)**

Clinical Pharmacology - NDA Filing Memo

NDA:	**21-344/SE-12 IND: 52,121**
Compound:	**FASLODEX® (fulvestrant) 500 mg IM injection**
Sponsor:	**AstraZeneca**
Filing Date:	**December 14, 2009**
Reviewer:	**Young-Jin Moon, Ph.D.**

Background and Mechanism of action: The current submission is the supplement NDA which provides safety and efficacy information to support a dose change from the currently approved 250 mg dose to a 500 mg dose. It also provides for changes to the secondary packaging for the 500 mg dose and how these changes affect the CMC file, as well as the use of an additional alternate site for the secondary packaging of Faslodex.

The proposed indication for fulvestrant 500 mg is the same as the currently approved indication for fulvestrant 250 mg, i.e. the treatment of postmenopausal women (b) (4) with (b) (4) metastatic breast cancer who have been previously treated with an antiestrogen, (b) (4) It is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner and induces a rapid loss of ERα protein from breast cancer cells.

Clinical Studies: The applicant conducted 5 clinical studies (Table 1).

TABLE 1. Clinical studies

Study	Study design	Objectives (primary)	Treatment groups[a] (number of patients)
Pivotal phase III study pertinent to the proposed dose regimen and indication			
CONFIRM (D6997C00002)	Randomised, double blind, parallel group, multicentre	Efficacy and safety (TTP)	Fulvestrant 500 mg (362) Fulvestrant 250 mg (374)
Phase II studies pertinent to the proposed dose regimen and indication			
FINDER1 (D6997C00004)	Randomised, double blind, parallel group, Multicentre in Japan	Efficacy, PK and safety (ORR)	Fulvestrant 500 mg (47) Fulvestrant 250 mg (45) Fulvestrant 250 mg +LD (51)
FINDER2 (D6997C00006)	Randomised, double blind, parallel group, Multicentre In Western Countries	Efficacy, PK and safety (ORR)	Fulvestrant 500 mg (46) Fulvestrant 250 mg (47) Fulvestrant 250 mg +LD (51)
Other phase II studies not directly relevant to the evaluation of efficacy in the proposed indication			
NEWEST (D6997C00003)	Randomised, open label, mutlicentre	Efficacy, PK, PD and safety (Ki67 LI)	Fulvestrant 500 mg (109) Fulvestrant 250 mg (102)
FIRST (D6995C00006)	Randomised, open label, parallel group, multicentre	Efficacy and safety (CBR)	Fulvestrant 500 mg (102) Anastrozole 1 mg (103)

Pharmacometrics

The PK of fulvestrant at 500 mg was characterized using a population modeling approach in three phase 2 studies- FINDER 1, FINDER 2, and NEWEST. One population PK analysis report was found in the current submission. The phase 2 study was conducted in Japanese postmenopausal women with

estrogen receptor positive advanced breast cancer progressing or relapsing after previous endocrine therapy. The dataset contained 70 patients who received fulvestrant as either 250 mg monthly, 250 mg + LD or 500 mg intramuscular injections: 25, 21 and 24 patients, respectively. PK parameters obtained from this analysis were compared to the ones in Western patients in studies 9238IL/0021, 9238IL/0020 and 9238IL/0065 which were included in original NDA submission.

Pharmacogenomics
Study NEWEST (D6997C00003) compared the effects of fulvestrant 500 mg and 250 mg on the proliferation marker Ki67 after 4 weeks of treatment and assessed the PD markers of down-regulation and proliferation and the correlation between changes in Ki67 labeling index and changes in ER expression and progesterone-receptor (PgR) expression. The results did not contribute to PD portion of insert.

Recommendation: The Office of Clinical Pharmacology/Division of Pharmaceutical Evaluation 5 finds that NDA 21-344 is fileable. A pharmacometrics consult was submitted on 11/20/2009.

Actions: None needed.

Signatures

Young-Jin Moon	Brian P. Booth
Reviewer	Deputy Division Director
Division of Clinical Pharmacology 5	Division of Clinical Pharmacology 5

Cc: DDOP: CSO - **A Davis-Warren;** MTL - **A Ibrahim**; MO - **T Prowell**
DCP-5: Reviewer - **Y Moon, N Mehrotra;** PM TL - **C Tornoe;**
Deputy DD TL - **B Booth;** DD - **A Rahman**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

YOUNG J MOON
12/14/2009

BRIAN P BOOTH
12/16/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s012

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Date: August 26, 2010

To: Alberta Davis-Warren, Project Manager, Division of Drug Oncology Products (DDOP)

From: Keith Olin, Professional Regulatory Reviewer
Stephanie Victor, Direct-to-Consumer Regulatory Reviewer
Division of Drug Marketing, Advertising, and Communications, (DDMAC)

Subject: NDA 021344/SE-012
DDMAC labeling comments for Faslodex (fluvestrant) injection

PI review:
In response to your consult request, DDMAC have reviewed the August 9, 2010 version of the draft Package Insert (PI) for Faslodex. Please note recommended DDMAC changes for the PI were discussed at the August 9, 2010, and August 23, 2010 labeling meetings and appropriate changes were incorporated into the PI portion of the label.

Additional DDMAC comments are as follows:

Comparison of FASLODEX 250 mg and Anastrozole 1 mg in Combined Trials (Studies 2 and 3)

(b) (4)

PPI review:
DDMAC has reviewed the proposed August 9, 2010, version of the PPI for Faslodex and offer the following comments:

FDA-Approved Patient Labeling
PATIENT INFORMATION

4 page(s) of draft labeling have been withheld in full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

KEITH J OLIN
08/30/2010

STEPHANIE L VICTOR
08/30/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 16, 2010
To:	Robert Justice, MD Director, Division of Drug Oncology Products (DDOP)
Through:	Todd Bridges, RPh, Team Leader Kellie Taylor, PharmD, MPH, Associate Director Division of Medication Error Prevention and Analysis
From:	Denise V. Baugh, PharmD, BCPS, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Faslodex (Fulvestrant) Injection 250 mg/5 mL
Application Type/Number:	NDA# 021344
Applicant:	AstraZeneca Pharmaceuticals, LP
OSE RCM #:	2009-2357

1 INTRODUCTION

This review is written in response to a request from the Division of Drug Oncology Products for assessment of the container label, carton and insert labeling submitted as part of an efficacy supplement dated November 12, 2009. The label and labeling were revised to support a change in dosing regimen from 250 mg (given as a single 5 mL injection) intramuscularly once per month to 500 mg (given as two 5 mL injection of 250 mg each) intramuscularly on days 1, 15, and 29 then monthly thereafter. The current packaging configuration is a single 250 mg/5 mL syringe. (b) (4)

(b) (4)

Furthermore, a dose modification has been added to the insert labeling for patients with moderate hepatic impairment.

1.1 REGULATORY HISTORY

Faslodex (Fulvestrant) was approved on April 25, 2002. In correspondence dated (b) (4)

(b) (4)

2 PRODUCT INFORMATION

Faslodex (Fulvestrant) is an injection indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy. It is given intramuscularly. The proposed changes to be made are the dosing regimen as well as the packaging configuration for this drug product. The proposed changes to the dosing regimen are as follows:

Table 1. The current and proposed dosing regimens

Currently Marketed Dosing Regimen	Proposed Dosing Regimen
250 mg given intramuscularly into the buttock at intervals of one month as a single 5 mL injection.	500 mg given intramuscularly on days 1, 15, and 29 then once monthly thereafter (b) (4) over 1 to 2 minutes.

Table 2. The current and proposed packaging configurations

Currently Marketed 'How Supplied'	Proposed 'How Supplied'
One clear neutral glass barrel containing 250 mg/5 mL (50 mg/mL) injection for intramuscular injection; The syringes are presented in a tray with polystyrene plunger rod and safety needles (SafetyGlide™) for connection to the barrel.	(b) (4) (b) (4) The syringes are presented in a tray with polystyrene plunger rod and safety needles (SafetyGlide™) for connection to the barrel.

Faslodex should be refrigerated at 2° to 8° C (36° to 46° F). The product should also be protected from light and stored in the original container until time of use.

Per correspondence from the Applicant dated May 21, 2010, the currently marketed carton containing the single 250 mg/5 mL syringe (b) (4)
(b) (4)

3 METHODS AND MATERIALS REVIEWED

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

In our previous review (OSE# 01-0229-4 dated November 19, 2002), we retrieved a total of nine reports of medication errors through MedWatch and two quarterly reports submitted by AstraZeneca to fulfill a Phase IV commitment. Seven of the nine reports were related to confusion due to the labels/labeling of Faslodex. The errors were attributed to the similar appearance of the syringe labels, container labels and carton labeling for the 125 mg and 250 mg strengths. Additionally, there was confusion over the total milligram amount contained in each syringe which led to a dosing error and confusion with third party reimbursement. None of the patients experienced serious adverse events. Two of the nine reports identified concerns due to name similarity and confusion with Faslodex. One reporter expressed concern for confusion between the names, 'Faslodex' and 'Zoladex'. Another report identified a patient who referred to the dosage form of Faslodex as 'pills'. Further details were not provided.

The container label and carton labeling were revised according to our recommendations.

DMEPA conducted another search of the FDA Adverse Event Reporting System (AERS) database on January 19, 2010, for any medication errors which may have occurred since our previous review. We used the following criteria: Trade Name: Faslodex, Active Ingredient "Fulvestrant" and Verbatim Terms "Faslo%" and "Fulve%". The MedDRA reaction terms used were "Medication Errors" (HGLT) and "Product Quality Issues" (HLGT). There were no time frame restrictions for this search.

The reports were manually reviewed to determine if medication errors occurred involving factors related to either the packaging or labeling. Those cases that did not describe a medication error, and those that were determined to be irrelevant, were excluded from further analysis. Duplicate reports were grouped together into

cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

3.2 LABEL AND LABELING

For this product we reviewed the proposed container labels, carton and insert labeling submitted on November 12, 2009, as well as those that are currently marketed to assess the potential for confusion between these two presentations. DMEPA used Failure Mode and Effects Analysis (FMEA)[1] in our evaluation of the labels and labeling and their vulnerability to medication errors (see Appendices B and C).

4 RESULTS

4.1 AERS CASES

The AERS search retrieved a total of 6 medication error cases involving Faslodex which were reported since our last review (see Appendix A). The categories of medication errors include: wrong dose (n = 2), wrong drug (n = 2), wrong frequency (n = 1) and wrong technique (n = 1). One case involved both wrong dose and wrong frequency errors which explains the reason for six cases but seven errors reported.

4.1.1 Wrong Dose (N = 2)

In one case the patient received two 250 mg injections instead of the prescribed one injection. The patient complained of injection site pain and out pouching. Contributing factors were not stated. In the second case the patient received 500 mg initially, then 250 mg injections every 2 weeks for 2 doses. The reporter states that the medication error was the result of misinformation provided by a sales representative. The outcome was not stated.

4.1.2 Wrong Drug (N = 2)

In one case Zometa and Faslodex were inadvertently ordered and given for a patient when the intent was for the administration of Zometa alone. No details regarding the reason for the confusion were stated but the patient experienced no adverse events. In the other case a patient received Lupron in error instead of Faslodex. No contributing factors were stated regarding the reason for this medication error and the patient's condition was unknown at the time of the report.

4.1.3 Wrong Frequency (N = 2)

One case involved wrong frequency in which the reporter accidentally received injections one week apart. No outcome was stated nor contributing factors provided. The second case is cited above in Section 4.1.1 in which a patient received 500 mg initially, then 250 mg injections every 2 weeks for 2 doses. The reporter states that the medication error was the result of misinformation provided by a sales representative. The outcome was not stated.

4.1.4 Wrong technique (N = 1)

One case involved wrong technique in which a reporter states her mother was given the injection in the "wrong place". The reporter further states that the patient had a "cyst under her skin on (the) upper hip area where medication was injected". Further details were not provided

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

5 DISCUSSION AND RECOMMENDATIONS

DMEPA's review of the labels and labeling did not identify any vulnerability that could be attributed to medication error reports retrieved in AERS. However, we noted areas where information on the labels and labeling can be clarified and improved upon to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 5.1, *Comments to the Division,* for discussion during the review team's label and labeling meetings. Section 5.2, *Comments to the Applicant,* contains our recommendations for the container label and carton labeling. We request these recommendations in Section 5.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarification, please contact Sarah Simon, OSE Regulatory Project manager, at 301-796-5205.

5.1 COMMENTS TO THE DIVISION

The comments below were accepted by the Division during labeling meetings but are offered here for reference.

5.1.1 Insert Labeling

A. We note the use of the abbreviation, (b) (4) in the labeling which is considered error-prone[2]. This abbreviation can be misinterpreted as (b) (4) when written leading to a (b) (4) error. Additionally, FDA launched a campaign on June 14, 2006, warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols. As part of this campaign, FDA agreed to not include such abbreviations in our approved labeling because these abbreviations can be carried over to prescribing. Thus, we request that the Divisions not approve or use such symbols in their labels and labeling.

B. The descriptions of the two packaging configurations in Section 16 (How Supplied/Storage and Handling) (b) (4) Please revise both statements to read, "Faslodex is supplied as two (one) clear, neutral glass (Type 1) barrel(s) containing 250 mg/5 mL of Faslodex solution for intramuscular injection and fitted with a tamper evident closure".

C. We note that the Applicant refers to the Patient Labeling (Section 17.3) as a (b) (4) at the end of this section. This terminology is incorrect.

5.2 COMMENTS TO THE APPLICANT

5.2.1 General Comments

A. We recommend at the time of product launch you inform healthcare practitioners about the new dosing regimen and new packaging configuration for Faslodex.

B. Revise the statement (b) (4) to read 'Both syringes must be administered to receive the 500 mg dose' throughout the label and labeling. (b) (4) (b) (4).

[2] Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at http://www.ismp.org/Tools/confuseddrugnames.pdf

5.2.2 Carton Labeling

A. We note that the font used for certain information is presented [redacted]. Thus, important information is [redacted].

B. The statement on the side panels currently states, [redacted] revise this statement to read 'Both syringes must be administered to receive the 500 mg dose'.

C. The statement on the back of the carton labeling, 'Both syringes must be administered to receive the 500 mg recommended (monthly) dose' should be [redacted].

D. The statement on the front of the carton labeling, 'Both syringes must be administered to receive the 500 mg recommended (monthly) dose' [redacted].

E. We recommend you revise the statement [redacted] to read 'Contains 2 pre-filled syringes'. Additionally, this statement should be [redacted].

F. Include a [redacted] on the proposed packaging configuration for six months.

G. The use of the abbreviation, [redacted] on the carton labeling (see 'This carton contains' statement) is considered error-prone. This abbreviation can be misinterpreted as [redacted] when written leading to a [redacted] Additionally, FDA launched a campaign on June 14, 2006, warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols. As part of this campaign, FDA agreed to not include such abbreviations in our approved labeling because these abbreviations can be carried over to prescribing. Revise [redacted].

6 REFERENCES

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. OSE Review 01-0229-4; Post-Marketing Safety Review – Faslodex (Fulvestrant) Injection; Roselle, N; November 19, 2002.

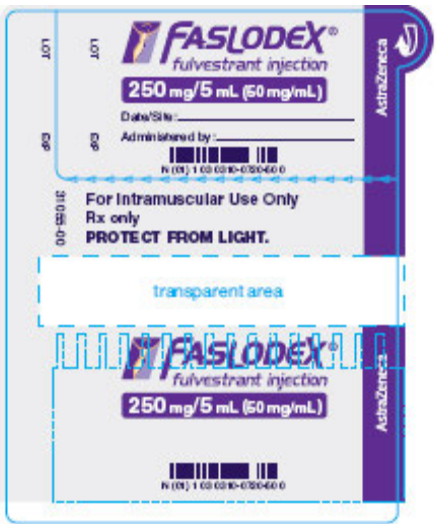
APPENDICES

Appendix A: Faslodex Medication Error ISR numbers

Wrong dose (n = 2) ISR #s
5360080-6, 5479479-2
Wrong drug (n = 2) ISR #s
4280382-4, 5216491-2
Wrong frequency (n = 2) ISR#s
41101555-4, 5479479-2
Wrong technique (n = 1) ISR#
5768089-5

2 Page(s) of draft labeling has been withheld in full as b4 (CCI/TS) immediately following this page

<u>Appendix C:</u> Current Carton Labeling and Container Label (from annual report submitted May 18, 2010)


FASLODEX®
fulvestrant injection
250 mg/5 mL (50 mg/mL)
Date/Site:
Administered by:
For Intramuscular Use Only
Rx only
PROTECT FROM LIGHT.
transparent area
AstraZeneca

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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

/s/

DENISE V BAUGH
08/16/2010

TODD D BRIDGES
08/16/2010

KELLIE A TAYLOR
08/16/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 4, 2010
To:	Robert Justice, MD, Dirctor
	Division of Drug Oncology Products (DDOP)
Through:	Mary Willy, PhD, Deputy Director
	Division of Risk Management (DRISK)
	LaShawn Griffiths, MSHS-PH, BSN, RN
	Senior Patient Labeling Reviewer, Acting Team Leader
	Division of Risk Management
From:	Sharon R. Mills, BSN, RN, CCRP
	Senior Patient Labeling Reviewer, Acting Team Leader
	Division of Risk Management
Subject:	DRISK Review of Patient Labeling (Patient Package Insert)
Drug Name(s):	Faslodex (fulvestrant) Injection
Application Type/Number:	NDA 21-344
Submission Number:	S-012
Applicant/sponsor:	AstraZeneca Pharmaceuticals
OSE RCM #:	2009-2367

1 INTRODUCTION

This review is written in response to a request by the Division of Drug Oncology Products (DDOP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for Faslodex (fulvestrant).

AstraZeneca Pharmaceuticals received original approval of their New Drug Application, NDA 21-344 for Faslodex (fulvestrant) Injection, on April 25, 2002. Faslodex is indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. The Applicant submitted an Efficacy Supplement sNDA21-344/012 on November 12, 2009 which provides safety and efficacy information to support a proposed dose change. The Prescribing Information is also being converted to the Physicians Labeling Rule (PLR) format with this supplement.

2 MATERIAL REVIEWED

- Draft Faslodex (fulvestrant) Injection Prescribing Information (PI) submitted November 12, 2009, revised by the Review Division throughout the current review cycle and provided to DRISK on July 23, 2010.
- Draft Faslodex (fulvestrant) Patient Package Insert (PPI) submitted on November 12, 2009, revised by the review division throughout the review cycle and provided to DRISK on July 23, 2010.

3 RESULTS OF REVIEW

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- rearranged information due to conversion of the PI to PLR format
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please send our comments to the Applicant. Let us know if DDOP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

Please let us know if you have any questions.

10 page(s) of draft labeling have been withheld in full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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

/s/

SHARON R MILLS
08/04/2010

MARY E WILLY
08/04/2010
I concur

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 021344 BLA#	NDA Supplement #:S- 012 BLA STN #	Efficacy Supplement Type SE- 02
Proprietary Name: Faslodex Injection Established/Proper Name: Fulvestrant Dosage Form: Solution for injection Strengths: 250 mg/ 5 ml		
Applicant: AstraZeneca Uk Limited Agent for Applicant (if applicable):		
Date of Application: November 12, 2009 Date of Receipt: November 12, 2009 Date clock started after UN:		
PDUFA Goal Date: September 13, 2010	Action Goal Date (if different):	
Filing Date: January 13, 2010	Date of Filing Meeting: December 14, 2009	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Breast Cancer/Change dose from 250 mg to 500 mg. Also provides for changes to the secondary packaging for the 500 mg does, as well as the use of an additional site for the secondary packaging of FASLODEX® (fulvestrant) 250 mg/5 ml (50 mg/ml) Sterile Solution for injection		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: Efficacy ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)
Review Classification ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41)

Other:	☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s):	

Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☐ Not in arrears ☐ In arrears
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*	

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:		X		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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

Exclusivity	YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*			**X**	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				

Forms and Certifications				
***Electronic** forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included. **Forms** include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?				
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:** Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:** Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	X			

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		X		

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***			X	Efficacy supplement
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***				

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** January 24, 1997 September 17, 2003 ***If yes, distribute minutes before filing meeting***	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** October 1, 2009 August 3, 2000 November 9, 2000 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** February 14, 2008 (CAC) ***If yes, distribute letter and/or relevant minutes before filing meeting***	X			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 14, 2009

BLA/NDA/Supp #: 021344

PROPRIETARY NAME: Faslodex Injection

ESTABLISHED/PROPER NAME: Fulvestrant

DOSAGE FORM/STRENGTH: Solution for injection/ 250 mg/5 ml

APPLICANT: AstraZeneca UK Limited

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): 1. For Metastatic Breast Cancer indication/ proposes to change dose from 250 mg to 500 mg. 2. Propose to change the secondary packaging for the 500 mg dose and how these changes affect the CMC file. 3. Proposes the use of an additional alternate site for the secondary packaging of FASLODEX (fulvestrant) 250 mg/ 5 ml (50 mg/ml) sterile solution for injections.

PDUFA date: September 13, 2010

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alberta Davis-Warren	Y
	CPMS/TL:	Alice Kacuba	N
Cross-Discipline Team Leader (CDTL)	Ibrahim		Y
Clinical	Reviewer:	Tatiana Prowell	Y
	TL:	Amna Ibrahim	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		

	TL:		
Clinical Pharmacology	Reviewer:	Young-Jin Moon	Y
	TL:	Julie Bullock/Brian Booth	Y
Biostatistics	Reviewer:	Xiaoping (Janet) Jiang	Y
	TL:	Kun He	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Kimberly Ringgold	Y
	TL:	Haleh Saber	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Hamid Shafiei	Y
	TL:	Liang Zhou	N
Quality Microbiology *(for sterile products)*	Reviewer:	Denise Miller	Y
	TL:		
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Pending	
	TL:		
OSE/DRISK (REMS)	Reviewer:	Pending	
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		

Other reviewers		
Other attendees		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**: data sets	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☐ Not Applicable ☐ YES ☒ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**: No comments	☐ Not Applicable ☒ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Alberta Davis-Warren **21st Century Review Milestones (see attached)** (optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

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

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

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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

/s/

ALBERTA E DAVIS WARREN
07/01/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s012

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 021344 SUPPL # 012 HFD # 150

Trade Name Faslodex Injection

Generic Name Fulvestrant

Applicant Name AstraZeneca UK Limited

Approval Date, If Known 09/13/10

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

SE2

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

YES ☒ NO ☐

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

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 ☒ NO ☐

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

3 years

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# 021344 (Parent 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 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

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

(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:

D6997C00002

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

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

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

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

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

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 ☐

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

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"):

D6997C00002

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 # 052121	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 ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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:

==========

Name of person completing form: Alberta Davis-Warren
Title: Regulatory Health Project Manager
Date: August 30, 2010

Name of Office/Division Director signing form: Amna Ibrahim, M.D.
Title: Deputy Director

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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

/s/

ALBERTA E DAVIS WARREN
08/30/2010

AMNA IBRAHIM
08/30/2010

Davis-Warren, Alberta E

From: Greeley, George
Sent: Monday, August 23, 2010 11:17 AM
To: Davis-Warren, Alberta E
Cc: Addy, Rosemary; Mathis, Lisa
Subject: NDA 21-344 Faslodex

Importance: High

Attachments: 1_Pediatric_Record.pdf

Hi Alberta,

The Faslodex (fulvestrant) full waiver was reviewed by the PeRC PREA Subcommittee on July 7, 2010.

The Division recommended a full waiver because the disease/condition does not exist in children

The PeRC agreed with the Division to grant a full waiver for this product. The pediatric record is attached as proof of the PeRC's review.

1 Pediatric_Record
df (62 KB)...

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

Organization: DDOP **Product Name: FASLODEX (FULVESTRANT)250MG/5ML INJ**

Appl Type No: NDA 21344 **Applicant: ASTRAZENECA PHARMACEUTICALS LP**

Submission Type #: SUPPL - 12 **Submission Status: PENDING**

FDA Received Date	Dosage Form	Orphan	Subm Status Date	Goal Due Date	Submission Classification/ Supplement Category Level Two	Submission Indication
11/13/2009	SOLUTION, INJECTION	N	11/13/2009	9/13/2010	DOSING	TREATMENT OF HORMONE RECEPTOR POSITIVE METASTATIC BREAST CANCER IN POSTMENOPAUSAL WOMEN WITH DISEASE PROGRESSION FOLLOWING ANTIESTROGEN THERAPY

Pediatric Record ID	PREA Study Status	Pediatric Category	Min Value	Max Value	Waiver/ Deferral Reason	Waiver/ Deferral Reason Explanation	Study Due Date
744	WAIVED	FULL	0	16	DISEASE/CONDITION DOES NOT EXIST IN CHILDREN		

1.3.3 DEBARMENT CERTIFICATION

Re: **NDA 21-344**

FASLODEX® (fulvestrant) Injection

Debarment Certification Statement

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

Sincerely,

Anthony Rogers, Vice President
US Regulatory Affairs
AstraZeneca

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 021344 BLA #	NDA Supplement # 012 BLA STN #	If NDA, Efficacy Supplement Type: SE2
Proprietary Name: Faslodex for Injection Established/Proper Name: Fulvestrant Dosage Form: Solution for Injection		Applicant: AstraZeneca Pharmaceuticals LP Agent for Applicant (if applicable):
RPM: Alberta E. Davis-Warren		Division: Division of Drug Oncology Products

NDAs:
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is September 13, 2010	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received

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

❖ Application Characteristics [2]

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

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

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	X
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 9-9-10
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	X
• Original applicant-proposed labeling	X
• Example of class labeling, if applicable	N/A

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in ttrack-changes format.	X
• Original applicant-proposed labeling	X
• Example of class labeling, if applicable	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	X
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	NA
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEPA 8-16-10 ☒ DRISK 8-4-10 ☒ DDMAC 8-30-10 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	07-1-10
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☒ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 7-7-10 If PeRC review not necessary, explain: _____ • Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☐ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	X
❖ Internal memoranda, telecons, etc.	X

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg October 1, 2009
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 9-7-10
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None See DD summary
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See DD summary
• Clinical review(s) *(indicate date for each review)*	8-30-10
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	X
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None 8-17-10
Statistical Review(s) *(indicate date for each review)*	☐ None 8-13-10
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 8-18-10
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 9-3-10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 8-4-10
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 4-21-10
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	8-4-10
☐ Review & FONSI *(indicate date of review)*	N/A
☐ Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: 8-26-10 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

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

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

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

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

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

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

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

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

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
09/09/2010

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Wednesday, September 08, 2010 12:14 PM
To: 'Walsh, Sally A'
Cc: 'Troise, Nicholas J'
Subject: FW: Faslodex NDA 021344 submission 9-7-2010 - Formatting revisions
Importance: High
Attachments: nonannotated-draft-label-09-07-10 .pdf

Dear Sally,

As per our conversation earlier today, please make the following formatting revisions to the package insert:

Thank you,
Alberta

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
301-796-3908
301-796-9845 fax
Alberta.Davis-Warren@fda.hhs.gov

From: Walsh, Sally A [mailto:sally.walsh@astrazeneca.com]
Sent: Tuesday, September 07, 2010 3:00 PM
To: Davis-Warren, Alberta E
Cc: Troise, Nicholas J

Subject: Faslodex NDA 021344 submission 9-7-2010

Hello Alberta,

As requested here is the nonannotated label that was submitted today through the gateway. I have also included the cover letter for your reference.

Kind regards,

Sally Walsh

Sally A. Walsh
Associate Director

AstraZeneca Pharmaceuticals
AstraZeneca Regulatory Affairs
C3B-101, 1800 Concord Pk, PO Box 15437
Wilmington, DE 19850-5437
Tel (b) (6) Mobile (b) (6)
Sally.Walsh@astrazeneca.com

25 page(s) of draft labeling have been withheld in full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
09/08/2010

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Tuesday, September 07, 2010 2:05 PM
To: Walsh, Sally A
Cc: 'Troise, Nicholas J'
Subject: NDA 021344 - Faslodex- Section 5.3 missing cross reference

Importance: High

Dear Sally,

Please add the following cross reference in section 5.3 (Use in Pregnancy) of the package insert:

[see Use in Specific Populations (8.1)]

Please contact me if you have any questions.

Thank you,
Alberta

Alberta E. Davis-Warren, B.S.
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
301-796-3908
301-796-9845 fax
Alberta.Davis-Warren@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
09/07/2010

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Tuesday, August 31, 2010 12:47 PM
To: 'Troise, Nicholas J'
Cc: Walsh, Sally A
Subject: RE: NDA 021344 Faslodex US PI and PPI Copy
Attachments: annotated-draft-label-08-26-10 (2).doc

Dear Nick,

We made a few more edits to the 8-26-10 annotated draft label, see sections 13.1 and 14. The revised changes to the patient package insert are acceptable.

If the additional edits to the package insert are acceptable, please send a clean version of the label. Please also combine the package insert and patient package insert into one document.

The revisions to the carton and container labels are acceptable; please send clean copies of the labels.

Please provide a response by this Thursday, September 2, 2010 at 12 pm (ET).

Thank you,
Alberta

Alberta E. Davis-Warren, B.S.
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
301-796-3908
301-796-9845 fax
Alberta.Davis-Warren@fda.hhs.gov

From: Troise, Nicholas J [mailto:Nicholas.Troise@astrazeneca.com]
Sent: Tuesday, August 31, 2010 10:56 AM
To: Davis-Warren, Alberta E
Cc: Walsh, Sally A
Subject: RE: NDA 021344 Faslodex US PI and PPI Copy

Thank you. I'll await your official request (as for previous requests) for all 'final' revisions to the package insert, before I ask the AZ team to meet.
Nick

From: Davis-Warren, Alberta E [mailto:Alberta.Davis-Warren@fda.hhs.gov]
Sent: Tuesday, August 31, 2010 10:53 AM

To: Troise, Nicholas J
Cc: Walsh, Sally A
Subject: RE: NDA 021344 Faslodex US PI and PPI Copy

Its a required change.

Thank you,
Alberta

From: Troise, Nicholas J [mailto:Nicholas.Troise@astrazeneca.com]
Sent: Tuesday, August 31, 2010 7:43 AM
To: Davis-Warren, Alberta E
Cc: Walsh, Sally A
Subject: RE: NDA 021344 Faslodex US PI and PPI Copy

Dear Alberta,

I apparently was having Outlook connectivity problems yesterday, since I did not receive your email until sometime after 5 pm yesterday, Aug 30.
I will wait to receive all of FDA's final review comments before I alert the AZ labeling review team for Faslodex.

(Is the comment, below, from the stats reviewer a 'required' change, or a recommendation?.....ie, *should* delete "(p-value=0.091)")

Thank you,
Nick

From: Davis-Warren, Alberta E [mailto:Alberta.Davis-Warren@fda.hhs.gov]
Sent: Monday, August 30, 2010 2:58 PM
To: Troise, Nicholas J
Cc: Walsh, Sally A
Subject: RE: NDA 021344 Faslodex US PI and PPI Copy

Dear Nick,

Please see the comment below regarding page 19 of the package insert:

[redacted] (b) (4)

Pharm/Tox is still reviewing the label, if there are additional revisions to the label; I will send the revised package insert tomorrow.

Thank you,
Alberta

From: Troise, Nicholas J [mailto:Nicholas.Troise@astrazeneca.com]
Sent: Thursday, August 26, 2010 4:21 PM
To: Davis-Warren, Alberta E
Cc: Walsh, Sally A
Subject: FW: NDA 021344 Faslodex US PI and PPI Copy

Hi Alberta,

Here is the cover letter that accompanied today's submission (sequence # 0034) of the PI & PPI. Hopefully this should help the FDA interpret AZ's draft labeling revisions!

(Sorry, I forgot to include it previously.)

<<2010-08-26-cover-letter-response.pdf>>

Nick

Nicholas J Troise

Director

AstraZeneca

US Regulatory Affairs

C1C-123, 1800 Concord Pike

Wilmington, Delaware 19850

Tel (b) (6) Mobile (b) (6)

nicholas.troise@astrazeneca.com

Please consider the environment before printing this e-mail

From: Troise, Nicholas J
Sent: Thursday, August 26, 2010 2:19 PM
To: alberta.davis-warren@fda.hhs.gov
Cc: Walsh, Sally A
Subject: NDA 021344 Faslodex US PI and PPI Copy

Hi Alberta,

Attached is a courtesy copy of the draft US PI and the PPI section for Faslodex S-012. It was submitted via the gateway this afternoon.

<<annotated-draft-label-patient-information-08-26-10.doc>> <<annotated-draft-label-08-26-10.doc>>

As we discussed the packaging/carton labeling information that was submitted by AZ yesterday, Aug 25, has been received by FDA. If you decide that you want a courtesy

copy, please let me know.

Thank you,

Nick

Nicholas J Troise

Director

AstraZeneca

US Regulatory Affairs

C1C-123, 1800 Concord Pike

Wilmington, Delaware 19850

Tel (b) (6) Mobile (b) (6)

nicholas.troise@astrazeneca.com

Please consider the environment before printing this e-mail

26 page(s) of draft labeling have been withheld in full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-7	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
08/31/2010

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Monday, August 30, 2010 2:58 PM
To: 'Troise, Nicholas J'
Cc: Walsh, Sally A
Subject: RE: NDA 021344 Faslodex US PI and PPI Copy

Dear Nick,

Please see the comment below regarding page 19 of the package insert:

[redacted] (b) (4)

Pharm/Tox is still reviewing the label, if there are additional revisions to the label; I will send the revised package insert tomorrow.

Thank you,
Alberta

From: Troise, Nicholas J [mailto:Nicholas.Troise@astrazeneca.com]
Sent: Thursday, August 26, 2010 4:21 PM
To: Davis-Warren, Alberta E
Cc: Walsh, Sally A
Subject: FW: NDA 021344 Faslodex US PI and PPI Copy

Hi Alberta,

Here is the cover letter that accompanied today's submission (sequence # 0034) of the PI & PPI. Hopefully this should help the FDA interpret AZ's draft labeling revisions!

(Sorry, I forgot to include it previously.)

<<2010-08-26-cover-letter-response.pdf>>

Nick

Nicholas J Troise

Director

AstraZeneca

US Regulatory Affairs

C1C-123, 1800 Concord Pike

Wilmington, Delaware 19850

Tel (b) (6) Mobile (b) (6)

nicholas.troise@astrazeneca.com

Please consider the environment before printing this e-mail

From: Troise, Nicholas J
Sent: Thursday, August 26, 2010 2:19 PM
To: alberta.davis-warren@fda.hhs.gov
Cc: Walsh, Sally A
Subject: NDA 021344 Faslodex US PI and PPI Copy

Hi Alberta,

Attached is a courtesy copy of the draft US PI and the PPI section for Faslodex S-012. It was submitted via the gateway this afternoon.

<<annotated-draft-label-patient-information-08-26-10.doc>> <<annotated-draft-label-08-26-10.doc>>

As we discussed the packaging/carton labeling information that was submitted by AZ yesterday, Aug 25, has been received by FDA. If you decide that you want a courtesy

copy, please let me know.

Thank you,

Nick

Nicholas J Troise

Director

AstraZeneca

US Regulatory Affairs

C1C-123, 1800 Concord Pike

Wilmington, Delaware 19850

Tel (b) (6) Mobile (b) (6)

nicholas.troise@astrazeneca.com

Please consider the environment before printing this e-mail

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
08/30/2010

Davis-Warren, Alberta E

From: Baugh, Denise
Sent: Thursday, August 26, 2010 5:25 PM
To: Davis-Warren, Alberta E; Ibrahim, Amna; Prowell, Tatiana; Morin, Steve; Mills, Sharon; Moon, Young-Jin; Bullock, Julie; Mehrotra, Nitin; Garnett, Christine; Shafiei, Hamid; Patel, Hasmukh B; Bridges, Todd; Saber, Haleh; Ringgold, Kimberly
Cc: Simon, Sarah
Subject: RE: NDA 021344 Faslodex US PI and PPI Copy

Alberta,
The container label, carton labeling and insert labeling are all acceptable. I have no further comments at this time.
Thanks.

Denise B

From: Davis-Warren, Alberta E
Sent: Thursday, August 26, 2010 3:29 PM
To: Ibrahim, Amna; Prowell, Tatiana; Morin, Steve; Mills, Sharon; Moon, Young-Jin; Bullock, Julie; Mehrotra, Nitin; Garnett, Christine; Shafiei, Hamid; Patel, Hasmukh B; Baugh, Denise; Bridges, Todd; Saber, Haleh; Ringgold, Kimberly
Cc: Simon, Sarah
Subject: FW: NDA 021344 Faslodex US PI and PPI Copy
Importance: High

Dear All,

Please see the attached labels from the sponsor. Please let me know if the labels are acceptable or if more revisions are needed.

Thank you,
Alberta

From: Troise, Nicholas J [mailto:Nicholas.Troise@astrazeneca.com]
Sent: Thursday, August 26, 2010 2:19 PM
To: Davis-Warren, Alberta E
Cc: Walsh, Sally A
Subject: NDA 021344 Faslodex US PI and PPI Copy

Hi Alberta,

Attached is a courtesy copy of the draft US PI and the PPI section for Faslodex S-012. It was submitted via the gateway this afternoon.

<<annotated-draft-label-patient-information-08-26-10.doc>> <<annotated-draft-label-08-26-10.doc>>

As we discussed the packaging/carton labeling information that was submitted by AZ yesterday, Aug 25, has been received by FDA. If you decide that you want a courtesy

copy, please let me know.

Thank you,

Nick

Nicholas J Troise

Director

_____

AstraZeneca

US Regulatory Affairs

C1C-123, 1800 Concord Pike

Wilmington, Delaware 19850

Tel (b) (6) Mobile (b) (6)

nicholas.troise@astrazeneca.com

Please consider the environment before printing this e-mail

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
08/30/2010

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Tuesday, August 24, 2010 11:17 AM
To: Troise, Nicholas J
Cc: 'Walsh, Sally A'
Subject: NDA 021344/Faslodex- Revised labeling

Attachments: NDA 021344 annotated-draft-label-08-13-10-.doc; 8.23.10 NDA 021344 annotated-draft-label-patient-information-08-13-10-.doc

Dear Nick,

Attached are our revisions to the 8-13-10 submission. Please provide a response to the revisions by this Thursday, August 26, 2010 at 4 pm EDT. Please contact me if you have any questions.

NDA 021344
ınnotated-draft-lab..

8.23.10 NDA
21344 annotated-d.

Thank you,
Alberta

Alberta E. Davis-Warren, B.S.
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
301-796-3908
301-796-9845 fax
Alberta.Davis-Warren@fda.hhs.gov

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
08/24/2010

Davis-Warren, Alberta E

›m: Davis-Warren, Alberta E
›nt: Thursday, August 26, 2010 3:17 PM
To: Ibrahim, Amna; Prowell, Tatiana; Bullock, Julie; Moon, Young-Jin; Mehrotra, Nitin; Garnett, Christine; Shafiei, Hamid; Patel, Hasmukh B; Tang, Shenghui; He, Kun; Sridhara, Rajeshwari; Miller, Denise; Langille, Stephen; Mills, Sharon; Willy, Mary E; Baugh, Denise; Bridges, Todd; Taylor, Kellie; Olin, Keith; Victor, Stephanie; Saber, Haleh; Ringgold, Kimberly; Jiang, Xiaoping (Janet)
Subject: Faslodex NDA 021344/SE2-012 FDAAA Employee List

Follow Up Flag: Follow up
Due By: Wednesday, August 25, 2010 12:00 AM
Flag Status: Flagged

Hello Everyone,

According to FDAAA, each approval action requires a list of employees that participated in the action. Do you want your name associated with the approval of this supplement. You either authored or co-signed a review. Please use the voting button to either consent or object to be included in the list.

This supplement provides for changing dose from 250 mg dose to 500 mg dose.

Thank you,
Alberta

Alberta E. Davis-Warren, B.S.
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
301-796-3908
301-796-9845 fax
Alberta.Davis-Warren@fda.hhs.gov

Tracking:

Recipient	Delivery	Response
Ibrahim, Amna	Delivered: 8/26/2010 3:17 PM	Consent: 8/26/2010 3:17 PM
Prowell, Tatiana	Delivered: 8/26/2010 3:17 PM	Consent: 8/30/2010 7:38 AM
Bullock, Julie	Delivered: 8/26/2010 3:17 PM	Consent: 8/27/2010 7:22 AM
Moon, Young-Jin	Delivered: 8/26/2010 3:17 PM	Consent: 8/26/2010 3:17 PM
Mehrotra, Nitin	Delivered: 8/26/2010 3:17 PM	Consent: 8/26/2010 3:25 PM
Garnett, Christine	Delivered: 8/26/2010 3:17 PM	
Shafiei, Hamid	Delivered: 8/26/2010 3:17 PM	
Patel, Hasmukh B	Delivered: 8/26/2010 3:17 PM	Consent: 8/26/2010 3:21 PM
Tang, Shenghui	Delivered: 8/26/2010 3:17 PM	Consent: 8/26/2010 3:17 PM
He, Kun	Delivered: 8/26/2010 3:17 PM	
Sridhara, Rajeshwari	Delivered: 8/26/2010 3:17 PM	Consent: 8/26/2010 3:18 PM
Miller, Denise	Delivered: 8/26/2010 3:17 PM	Consent: 8/26/2010 3:20 PM
Langille, Stephen	Delivered: 8/26/2010 3:17 PM	Object: 8/26/2010 8:14 PM
Mills, Sharon	Delivered: 8/26/2010 3:17 PM	Object: 8/26/2010 4:32 PM
Willy, Mary E	Delivered: 8/26/2010 3:17 PM	Object: 8/30/2010 8:50 AM
Baugh, Denise	Delivered: 8/26/2010 3:17 PM	Consent: 8/26/2010 3:17 PM
Bridges, Todd	Delivered: 8/26/2010 3:17 PM	Consent: 8/26/2010 4:08 PM
Taylor, Kellie	Delivered: 8/26/2010 3:17 PM	
Olin, Keith	Delivered: 8/26/2010 3:17 PM	

Recipient	Delivery	Response
Victor, Stephanie	Delivered: 8/26/2010 3:17 PM	Consent: 8/27/2010 5:51 AM
Saber, Haleh	Delivered: 8/26/2010 3:17 PM	Consent: 9/1/2010 8:40 AM
Ringgold, Kimberly	Delivered: 8/26/2010 3:17 PM	Consent: 8/26/2010 3:51 PM
Jiang, Xiaoping (Janet)	Delivered: 8/26/2010 3:17 PM	Consent: 8/26/2010 4:46 PM

MEMORANDUM OF TELECON

DATE: August 12, 2010

APPLICATION NUMBER: NDA 021344

BETWEEN:
Name: Justin P O Lindemann MBChB BSc MBA, Medical Science Director
Franco Guzman, MD, Sr Medical Scientist
Tanya Coleman, Clinical Pharmacology & DMPK Project Leader
Nick Troise, Director, Regulatory Affairs
Sally Walsh, Associate Director, Regulatory Affairs
Cindy Lancaster, Executive Director, Regulatory Portfolio Leader
Merran Macpherson, Clinical Pharmacokineticist
Michele Samluk Medori, Labeling Manager

Phone: (b) (4)
Representing: AstraZeneca UK Limited

AND

Division of Drug Oncology Products, HFD-150
Name: Amna Ibrahim, MD, Deputy Division Director, DDOP
Tatiana Prowell, MD, Medical Officer, DDOP
Julie Bullock, PharmD, Clinical Pharmacology Team leader
Nitin Mehrotra, PhD, Pharmacometrics Reviewer
Alberta Davis-Warren, Regulatory Health Project Manager

SUBJECT: NDA 021344 Faslodex Package insert: Dosage and Administration

HISTORY: On November 12, 2009 the Sponsor submitted an efficacy supplement to change the dosage of the drug from 250 mg to 500 mg. On August 9, 2010 the Division sent the FDA revised labeling to the Sponsor. On August 10, 2010 the Sponsor requested a labeling T-con "to gain clarity regarding the FDA's proposed language for the PK information and section 2.2 Dose modification."

TODAY'S PHONE CALL: Please see summary below provided by the Clinical Pharmacology Review team:

1. Dose Adjustment in Hepatic Impairment:
Sponsor proposed (b) (4)

(b) (4)

FDA Response:

FDA stated that (b) (4)

On the other hand, plasma concentrations in a Child-Pugh B patient administered 250 mg dosing regimen will be in between the plasma concentrations produced by the 250 and 500 mg dosing regimen. Therefore, administering 250 mg dosing regimen to a Child-Pugh B patient seems to be an appropriate option.

As an alternative, FDA proposed that the sponsor could consider the option of an additional dose of 250 mg on Day 14 in Child-Pugh B patients to obtain concentrations near to the steady state concentrations within first month of dosing.

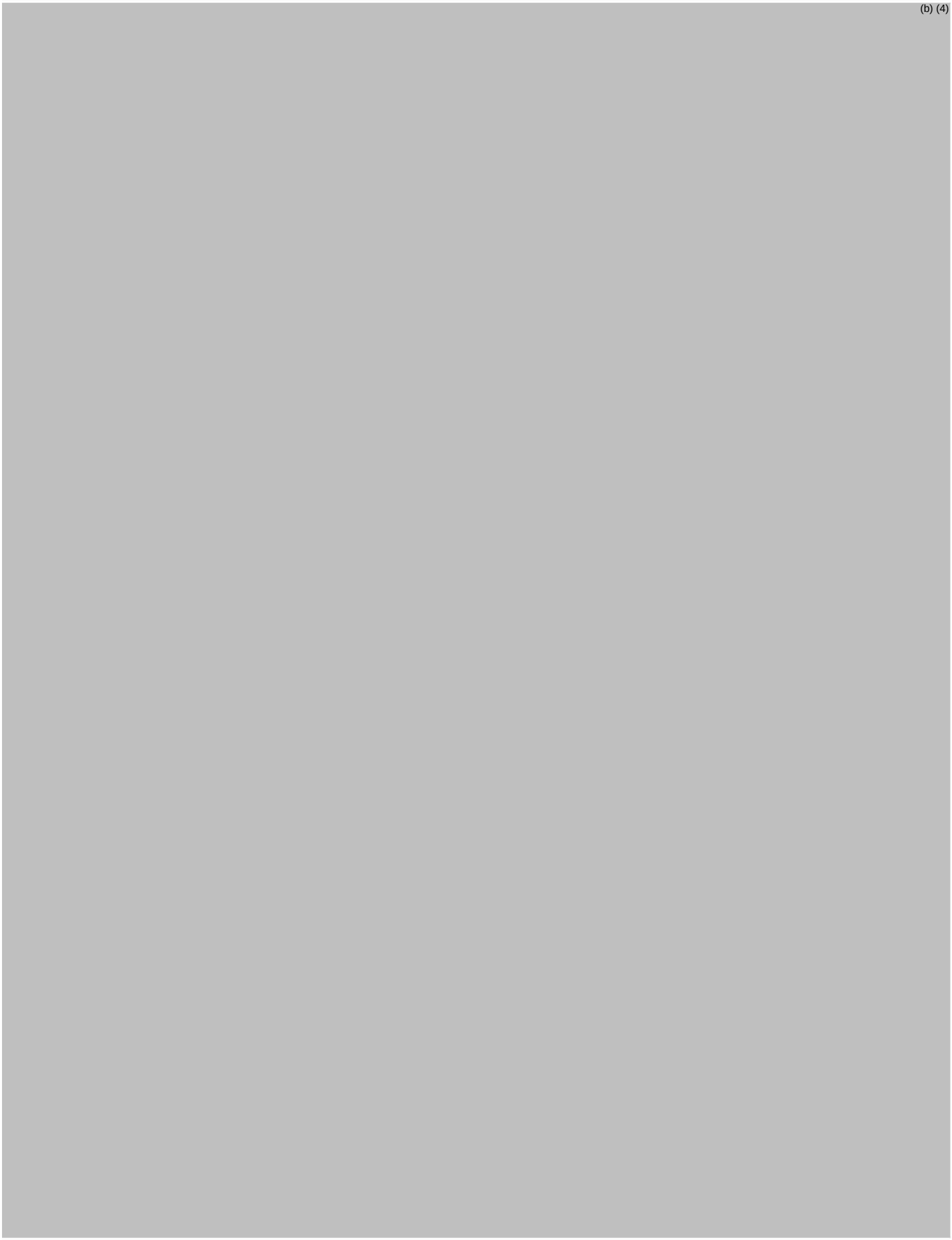
2. PK parameters in Table 3 under Section 12.3

There was discussion on PK parameter values (AUC, C_{max} and C_{min}) (b) (4)

FDA would accept PK parameters originally proposed by the sponsor.

Attachment: Figures 1 and 2

Alberta Davis-Warren, BS
Regulatory Health Project Manager


(b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
08/23/2010

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
5901-B Ammendale Road
Beltsville, Maryland 20705

To:	**Nicholas J. Troise**	**From:**	**Alberta Davis-Warren**
FAX/EMAIL	**Nicholas.Troise@astrazeneca.com**	**FAX:**	**301-796-9845**
Phone:	(b) (6)	**Phone:**	**301-796-3908**
Pages, including cover sheet: 3		**Date:**	**August 20, 2010**

RE: Information Requests for NDA 021344

Dear Mr. Troise

Please refer to your New Drug application (NDA 021344) for Faslodex® (fulvestrant) injection submitted on November 12, 2009. Please see the following comments from DMEPA:

General Comments:

A. We recommend at the time of product launch you inform healthcare practitioners about the new dosing regimen and new packaging configuration for Faslodex.

B. Revise the statement (b) (4) to read 'Both syringes must be administered to receive the 500 mg dose' throughout the label and labeling. (b) (4) (b) (4)

Carton Labeling:

A. We note that the font used for certain information is presented (b) (4) Thus, important information is (b) (4)

B. The statement on the side panels currently states, (b) (4) (b) (4) revise this statement to read 'Both syringes must be administered to receive the 500 mg dose'.

C. The statement on the back of the carton labeling, 'Both syringes must be administered to receive the 500 mg dose' should be (b) (4)

[redacted]

D. The statement on the front of the carton labeling, 'Both syringes must be administered to receive the 500 mg dose' is presented [redacted] placing a box around the statement.

E. We recommend you revise the statement [redacted] to read 'Contains 2 pre-filled syringes'. Additionally, this statement should be [redacted] This revised statement conveys [redacted]

F. Include a [redacted] on the proposed packaging configuration for six months.

G. The use of the abbreviation [redacted] on the carton labeling (see 'This carton contains' statement) is considered error-prone. This abbreviation can be misinterpreted as [redacted] when written leading to a [redacted] Additionally, FDA launched a campaign on June 14, 2006, warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols. As part of this campaign, FDA agreed to not include such abbreviations in our approved labeling because these abbreviations can be carried over to prescribing. Revise [redacted]

If the comments are acceptable please submit revised carton and container labeling in addition to the response to the comments.

Please respond to these requests by no later than August 25, 2010, at 12 PM EDT. Please submit an amendment to your application with your response to the requests using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) or FAX (301-796-9845) no later than August 25, 2010, at 12 PM EDT.

Thank you.
Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
CDER, FDA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
08/20/2010

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Monday, August 09, 2010 6:39 PM
To: 'Troise, Nicholas J'
Cc: 'Walsh, Sally A'
Subject: NDA 021344/Faslodex - Revised labeling and information request

Importance: High

Attachments: annotated-draft-label-08-06-10 JB.doc; clin pharm-rejecting their proposal.doc; 2010-0802 fulvestrant 21344 8-9-10 PPI marked up copy.doc

Dear Nick,

Attached are our revisions to the 8-6-10 submission. Also attached are Clin Pharm's rationale for rejecting your proposal and the revised PPI.


annotated-draft-lab
el-08-06-10...


clin pharm-rejecting
their pro...


2010-0802
ılvestrant 21344 8-.

Please also see this information request from the Clinical reviewer:

Please submit the CRFs for the following patients enrolled in the CONFIRM trial: Subject E0175025 and Subject E0100001.

Please provide a response to the revised labeling and the information request by this Thursday, August 12, 2010 at 12 PM (EDT).

Please contact me if you have any questions.

Thank you,
Alberta

Alberta E. Davis-Warren, B.S.
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
301-796-3908
301-796-9845 fax
Alberta.Davis-Warren@fda.hhs.gov

44 page(s) of draft labeling have been withheld in full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-7	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
08/10/2010

MEMORANDUM OF TELECON

DATE: July 26, 2010

APPLICATION NUMBER: NDA 021344

BETWEEN:
Name: Justin P O Lindemann MBChB BSc MBA, Medical Science Director
Franco Guzman, MD, Sr Medical Scientist
Mike P Harrison BSc, Clinical Pharmacology & DMPK Project Leader
Nick Troise, Director, Regulatory Affairs
Sally Walsh, Associate Director, Regulatory Affairs
Frances Kelleher, Ph.D., Global Regulatory Affairs Director

Phone: (b) (4)
Representing: AstraZeneca UK Limited

AND

Division of Drug Oncology Products, HFD-150
Name: Amna Ibrahim, MD, Deputy Division Director, DDOP
Tatiana Prowell, MD, Medical Officer, DDOP
Julie Bullock, PharmD, Clinical Pharmacology Team leader
Young-Jin Moon, PhD, Clinical Pharmacology Reviewer
Nitin Mehrotra, PhD, Pharmacometrics Reviewer
Hamid Shafiei, PhD, CMC Reviewer
Katherine DeLorenzo, MD, Medical Officer, DDOP
Alberta Davis-Warren, Regulatory Health Project Manager

SUBJECT: NDA 021344 Faslodex Package insert: Dosage and Administration

HISTORY: On November 12, 2009 the Sponsor submitted an efficacy supplement to change the dosage of the drug from 250 mg to 500 mg. On July 16, 2010 the Division sent the FDA revised labeling to the Sponsor to inform them of the Division's concept (b) (4)

(b) (4)

(b) (4) As a result of the question, the Division requested a teleconference with the Sponsor.

TODAY'S PHONE CALL: During the teleconference the Division conveyed to the Sponsor

(b) (4)

(b) (4)

As a result of the teleconference, the label will (b) (4) have the 500 mg dose.

Alberta Davis-Warren, BS
Regulatory Health Project Manager

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
08/10/2010

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Friday, July 30, 2010 4:27 PM
To: 'Troise, Nicholas J'
Cc: 'Walsh, Sally A'; Adams-Mclean, Allison
Subject: RE: NDA 021344 Faslodex - Revised labeling

Correction Thursday, August 5, 2010.

From: Davis-Warren, Alberta E
Sent: Friday, July 30, 2010 4:22 PM
To: Troise, Nicholas J
Cc: Walsh, Sally A; Adams-Mclean, Allison
Subject: NDA 021344 Faslodex - Revised labeling

Dear Nick,

Attached is our FDA revised labeling for NDA 021344/S-012 Faslodex. We are still reviewing the patient package insert; we will send it at a later time. Please review and please provide a response by Thursday, August 4, 2010 at 12 pm. I will be out of the office next week; LCDR Allison Adams-McLean is covering for me. She will forward your response to the team.

<< File: NDA 21344 CLINICAL 7-30-10 annotated-draft-label.doc >>

Thank you,
Alberta

Alberta E. Davis-Warren, B.S.
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
301-796-3908
301-796-9845 fax
Alberta.Davis-Warren@fda.hhs.gov

31 page(s) of draft labeling have been withheld in full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-7	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
07/30/2010

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Friday, July 16, 2010 4:45 PM
To: 'Troise, Nicholas J'
Cc: 'Walsh, Sally A'
Subject: RE: NDA 021344 - Faslodex Package insert - Dosage and administration

Sorry used the incorrect NDA number in the subject line, meant NDA 021344.
Alberta

From: Davis-Warren, Alberta E
Sent: Friday, July 16, 2010 4:44 PM
To: Troise, Nicholas J
Cc: 'Walsh, Sally A'
Subject: NDA 02344 - Faslodex Package insert - Dosage and administration

Dear Nick,

Our revisions to the dosage and administration section are quite different from what you proposed (see attached document). The supported sections are also included in the document. We are not asking you for a response to the revisions, this is just to inform you of our concept. Please contact me if you have any questions.

<< File: NDA 021344 Faslodex portions of package insert.doc >>

Thank you,
Alberta

Alberta E. Davis-Warren, B.S.
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
301-796-3908
301-796-9845 fax
Alberta.Davis-Warren@fda.hhs.gov

20 page(s) of draft labeling have been withheld in full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
07/18/2010

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
5901-B Ammendale Road
Beltsville, Maryland 20705

To:	**Nicholas J. Troise**	**From:**	**Alberta Davis-Warren**
FAX/EMAIL	**Nicholas.Troise@astrazeneca.com**	**FAX:**	**301-796-9845**
Phone:	(b) (6)	**Phone:**	**301-796-3908**
Pages, including cover sheet: 3		**Date:**	**July 2, 2010**

RE: Information Requests for NDA 021344

Dear Mr. Troise

Please refer to your New Drug application (NDA 021344) for Faslodex® (fulvestrant) injection submitted on November 12, 2009. During our review of the Clinical section of your submission, we have the following information requests:

We note that your proposed language for the Faslodex SLR states:
"Other adverse (b) (4) reported as drug-related and seen infrequently (<1%) include thromboembolic phenomena, myalgia, vertigo, leukopenia, (b) (4) and hypersensitivity reactions including angioedema and urticaria."

We also note that the approved label in Europe lists liver function abnormalities as a "very common" adverse reaction, defined as occurring in greater than 10% of Faslodex users.

The Integrated Summary of Safety for the Faslodex sNDA currently under review states:

"Elevations of liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST] and alkaline phosphatase [ALP]), an identified adverse drug reaction (ADR) for fulvestrant, were seen in both treatment groups. Post-baseline, ALT was increased by 1 CTC grade or more in approximately 16% of patients in each treatment group; AST was increased in 18.8% and 19.2% of patients in the fulvestrant 500 mg vs. 250 mg groups, respectively, and ALP was increased in approximately 19% of patients in each treatment group."

Table 44 in the Integrated Summary of Safety provides quantification of the percentage of patients from the pooled safety data with liver function abnormalities of grade 3 or greater, which occurred in up to 2.3% of subjects in the two arms.

(b) (4)

Please respond to these requests by no later than July 7, 2010, at 4 PM EDT. Please submit an amendment to your application with your response to the requests using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) or FAX (301-796-9845) no later than July 7, 2010, at 4 PM EDT.

Thank you.
Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
CDER, FDA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
07/02/2010

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
5901-B Ammendale Road
Beltsville, Maryland 20705

To:	**Nicholas J. Troise**	**From:**	**Alberta Davis-Warren**
FAX/EMAIL	**Nicholas.Troise@astrazeneca.com**	**FAX:**	**301-796-9845**
Phone:	(b) (6)	**Phone:**	**301-796-3908**
Pages, including cover sheet: 2		**Date:**	**June 18, 2010**

RE: Information Requests for NDA 021344

Dear Mr. Troise

Please refer to your New Drug application (NDA 021344) for Faslodex® (fulvestrant) injection submitted on November 12, 2009. During our review of the Clinical section of your submission, we have the following information requests:

Please provide the results of any available pertinent diagnostic laboratories, imaging, or consultations for CONFIRM trial Subject # E0240007 in association with the serious adverse event of hyperbilirubinemia.

Please respond to these requests by no later than June 23, 2010, at 12 PM EDT. Please submit an amendment to your application with your response to the requests using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) or FAX (301-796-9845) no later than June 23, 2010, at 12 PM EDT.

Thank you.
Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
CDER, FDA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
06/18/2010

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
5901-B Ammendale Road
Beltsville, Maryland 20705

To:	**Nicholas J. Troise**	**From:**	**Alberta Davis-Warren**
FAX/EMAIL	**Nicholas.Troise@astrazeneca.com**	**FAX:**	**301-796-9845**
Phone:	(b) (6)	**Phone:**	**301-796-3908**
Pages, including cover sheet: 2		**Date:**	**May 18, 2010**

RE: Information Requests for NDA 021344

Dear Mr. Troise

Please refer to your New Drug application (NDA 021344) for FASLODEX® (fulvestrant) injection submitted on November 12, 2009. During our review of your submission, we have the following information requests:

Information requests from OSE:

You are proposing (b) (4)

(b) (4)

Also, please send the container label and carton labeling for all currently marketed packaging configurations of Faslodex.

Please respond to these requests by no later than May 21, 2010 at 4:00 PM EDT. Please submit an amendment to your application with your response to the requests using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) or FAX (301-796-9845) no later than, May 21, 2010 at 4:00 PM EDT.

Thank you.
Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
CDER, FDA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
05/18/2010

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
5901-B Ammendale Road
Beltsville, Maryland 20705

To:	**Nicholas J. Troise**	**From:**	**Alberta Davis-Warren**
FAX/EMAIL	**Nicholas.Troise@astrazeneca.com**	**FAX:**	**301-796-9845**
Phone:	(b) (6)	**Phone:**	**301-796-3908**
Pages, including cover sheet: 3		**Date:**	**May 6, 2010**

RE: Information Requests for NDA 021344

Dear Mr. Troise

Please refer to your New Drug application (NDA 021344) for Faslodex® (fulvestrant) injection submitted on November 12, 2009. During our review of the Statistical section of your submission, we have the following information requests:

Were any patients (from the ITT population) with non-measurable disease at baseline classified as PD based solely upon progression on bone scan (i.e. without confirmation by another imaging modality)?

For those patients with non-measurable disease at baseline who experienced PD, please provide a dataset that includes the following variables, the dataset should be one record per patient.

Unique Patient id
Randomized treatment
Date of randomized
Date of TTP event/censoring
TTP Censor indicator
Months from randomization to earliest progression
Date of earliest progression
Date of PD confirmation
Method of assessment used for PD confirmation
Date of assessment that the date is used as date of TTP event/censoring
Date of death
Death Censor indicator

Please respond to these requests by no later than May 13, 2010 at 12 PM EDT. Please submit an amendment to your application with your response to the requests using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) or FAX (301-796-9845) no later than May 13, 2010, at 12 PM EDT.

Thank you.
Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
CDER, FDA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
05/06/2010

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
5901-B Ammendale Road
Beltsville, Maryland 20705

To:	**Nicholas J. Troise**	**From:**	**Alberta Davis-Warren**
FAX/EMAIL	**Nicholas.Troise@astrazeneca.com**	**FAX:**	**301-796-9845**
Phone:	(b) (6)	**Phone:**	**301-796-3908**
Pages, including cover sheet: 2		**Date:**	**May 3, 2010**

RE: Information Requests for NDA 021344

Dear Mr. Troise

Please refer to your New Drug application (NDA 021344) for FASLODEX® (fulvestrant) injection submitted on November 12, 2009. During our review of the Clinical section of your submission, we have the following information requests:

Please refer to Table 43 (Change from baseline to CTCAE >/= 3: clinical chemistry parameters) and data table 11.3.7.1.10 in the Clinical Study Report for the CONFIRM trial. Please submit the CRFs, and narratives if available, for all patients in the CONFIRM trial who experienced a grade 3 or greater increase in AST, ALT, or bilirubin (based upon either the laboratory dataset or the adverse event dataset).

Please respond to these requests by no later than May 10, 2010 at 12 PM EDT. Please submit an amendment to your application with your response to the requests using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) or FAX (301-796-9845) no later than May 10, 2010, at 12 PM EDT.

Thank you.
Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
CDER, FDA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
05/03/2010

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
5901-B Ammendale Road
Beltsville, Maryland 20705

To:	**Nicholas J. Troise**	**From:**	**Alberta Davis-Warren**
FAX/EMAIL	**Nicholas.Troise@astrazeneca.com**	**FAX:**	**301-796-9845**
Phone:	(b) (6)	**Phone:**	**301-796-3908**
Pages, including cover sheet: 2		**Date:**	**April 12, 2010**

RE: Information Requests for NDA 021344

Dear Mr. Troise

Please refer to your New Drug application (NDA 021344) for FASLODEX® (fulvestrant) injection submitted on November 12, 2009. During our review of your submission, we have the following information requests:

Please provide revised carton and container labels with the proposed dose change.

Also, please provide the status of the March 26, 2010 Statistical information request regarding the analyses of time to assessments.

Please respond to these requests by no later than April 13, 2010 at 5 PM EDT. Please submit an amendment to your application with your response to the requests using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) or FAX (301-796-9845) no later than April 13, 2010 at 5 PM EDT

Thank you.
Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
CDER, FDA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
04/12/2010

Davis-Warren, Alberta E

From: Davis-Warren, Alberta E
Sent: Tuesday, March 30, 2010 9:52 AM
To: 'Troise, Nicholas J'
Cc: Walsh, Sally A
Subject: RE: NDA 021344/FASLODEX - Information requests

Dear Nick,

Your interpretation is correct.

Thank you,
Alberta

From: Troise, Nicholas J [mailto:Nicholas.Troise@astrazeneca.com]
Sent: Monday, March 29, 2010 1:56 PM
To: Davis-Warren, Alberta E
Cc: Walsh, Sally A
Subject: RE: NDA 021344/FASLODEX - Information requests
Importance: High

Dear Alberta,

Re: NDA 021344 (S-012)

Information request # 1 refers to "all randomized patients". AstraZeneca is interpreting that to only pertain to all randomized patients in the single pivotal study D6997C00002 (CONFIRM).

Please confirm if our interpretation is correct, i.e., the Division is only expecting a response to question #1 for study D6997C00002.

Thank you,
Nick

Nicholas J Troise
Director

AstraZeneca
US Regulatory Affairs
C1C-123, 1800 Concord Pike
Wilmington, Delaware 19850
Tel (b) (6) Mobile (b) (6)
nicholas.troise@astrazeneca.com

From: Davis-Warren, Alberta E [mailto:Alberta.Davis-Warren@fda.hhs.gov]
Sent: Friday, March 26, 2010 1:57 PM
To: Troise, Nicholas J
Cc: Walsh, Sally A
Subject: NDA 021344/FASLODEX - Information requests

Dear Nick,

Please see the attached information request. Please provide a response as soon as possible.

<<Fax NDA 021344 IR 3-26-10.pdf>>

Thank you,
Alberta

Alberta E. Davis-Warren, B.S.
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
301-796-3908
301-796-9845 fax
Alberta.Davis-Warren@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
04/06/2010

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
5901-B Ammendale Road
Beltsville, Maryland 20705

To:	**Nicholas J. Troise**	**From:**	**Alberta Davis-Warren**
FAX/EMAIL	**Nicholas.Troise@astrazeneca.com**	**FAX:**	**301-796-9845**
Phone:	(b) (6)	**Phone:**	**301-796-3908**
Pages, including cover sheet: 3		**Date:**	**March 26, 2010**

RE: Information Requests for NDA 021344

Dear Mr. Troise

Please refer to your New Drug application (NDA 021344) for FASLODEX® (fulvestrant) injection submitted on November 12, 2009. During our review of the Statistical section of your submission, we have the following information requests:

Please respond to the following requests as soon as possible.

1. Please provide a dataset that contains the following variables for all randomized patients. This dataset should be one record per patient.

Unique Patient id
Randomized treatment
The date of discontinued randomized treatment
The date of withdrawn
The date of first subsequent therapy following discontinuation of the randomized treatment
Date of randomized
Date of TTP event/censoring
TTP Censor indicator
Date of death
Death Censor indicator
Which of assessment that the date is used as date of TTP event/censoring
All progression assessment (1^{st} , 2^{nd}, ..) need to be listed as:
[
Date of 1^{st} tumor assessment
Time from randomization to 1^{st} progress assessment
Progression disease indicator

…
]

2. Please fill in the following tables and provide the datasets and programs that are used to create the following tables.

Table 1. Mean and SD (in weeks or months) of Time to Assessment from Randomization

Time from randomization to	# (%)		Mean (SD)	
	Fulvestrant 500 mg (N=362)	**Fulvestrant 250 mg (N=374)**	**Fulvestrant 500 mg (N=362)**	**Fulvestrant 250 mg (N=374)**
1st Assessment				
2nd Assessment				
3rd Assessment				
4th Assessment				
…				

Table 2. Median (in weeks or months) of Time to Assessment from Randomization

Time from randomization to Assessment	**Fulvestrant 500 mg (N=362)**	**Fulvestrant 250 mg (N=374)**	**Log-rank Test**
1st Assessment			
2nd Assessment			
3rd Assessment			
4th Assessment			
…			

Please submit an amendment to your application with your response to the requests using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) or FAX (301-796-9845).

Thank you.
Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
CDER, FDA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
03/26/2010

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
5901-B Ammendale Road
Beltsville, Maryland 20705

To:	**Nicholas J. Troise**	**From:**	**Alberta Davis-Warren**
FAX/EMAIL	**Nicholas.Troise@astrazeneca.com**	**FAX:**	**301-796-9845**
Phone:	(b) (6)	**Phone:**	**301-796-3908**
Pages, including cover sheet: 2		**Date:**	**March 1, 2010**

RE: Information Requests for NDA 021344

Dear Mr. Troise

Please refer to your New Drug application (NDA 021344) for FASLODEX® (fulvestrant) injection submitted on January 21, 2010. During our review of your submission, we have the following information request:

Information request from CMC:

You have requested the categorical exclusion from environmental assessment (b) (4)

(b) (4)

Please respond to these requests by no later than Friday, March 5, 2010 at 12 PM EST. Please submit an amendment to your application with your response to the requests using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) or FAX (301-796-9845) no later than Friday, March 5, 2010 at 12 PM EST.

Thank you.
Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
CDER, FDA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
03/01/2010

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
5901-B Ammendale Road
Beltsville, Maryland 20705

To:	**Nicholas J. Troise**	**From:**	**Alberta Davis-Warren**
FAX/EMAIL	**Nicholas.Troise@astrazeneca.com**	**FAX:**	**301-796-9845**
Phone:	(b) (6)	**Phone:**	**301-796-3908**
Pages, including cover sheet: 2		**Date:**	**January 28, 2010**

RE: Information Requests for NDA 021344

Dear Mr. Troise

Please refer to your New Drug application (NDA 021344) for FASLODEX® (fulvestrant) injection submitted on November 12, 2009. During our review of the statistical section of your submission, we have the following information requests:

Regarding to Study d6997c00002, please provide names of variables, datasets and SAS programs that were used to obtain the following tables as soon as possible.

1) Table 14, Table 11.2.1.2, Table 18 and Table 26 in Clinical Study Report.

2) Table 1 and Table 11.2.1.10 in Clinical Study Report Addendum.

Please submit an amendment to your application with your response to the requests using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) or FAX (301-796-9845) as soon as possible.

Thank you.
Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
CDER, FDA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
01/28/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021344

FILING COMMUNICATION

AstraZeneca UK Limited
Attention: Nicholas J. Troise
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Troise:

Please refer to your new drug application (NDA) dated November 12, 2009, received November 13, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Faslodex Injection (fulvestrant), Solution for Injection and 250 mg/5 mL.

We also refer to your submission(s) dated November 16, 2009, December 22, 2009, December 23, 2009 and January 21, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is September 13, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate our initial proposed labeling and, if necessary, any postmarketing requirement/postmarketing commitment requests to you by approximately August 13, 2010.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We also request that you submit the following information:

Issues concerning your package insert:

HIGHLIGHTS OF PRESCRIBING INFORMATION:

1. Need to add Recent Major Changes in this section

FULL PRESCRIBING INFORMATION: CONTENTS*

2. Asterisk is needed next to CONTENTS in FULL PRESCRIBING INFORMATION: CONTENTS*
3. Indent subsection headings in the table of contents. Subsection headings should not be bolded and must be in regular font.

FULL PRESCRIBING INFORMATION:

4. Revise Pediatric Use Statement in section 8.4 to "Safety and effectiveness in pediatric patients have not been established."

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Alberta Davis-Warren, Regulatory Project Manager, at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALICE KACUBA
01/26/2010
Signing for Dr. Justice.

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF DRUG ONCOLOGY PRODUCTS
5901-B Ammendale Road
Beltsville, Maryland 20705

To:	**Nicholas J. Troise**	**From:**	**Alberta Davis-Warren**
FAX/EMAIL	**Nicholas.Troise@astrazeneca.com**	**FAX:**	**301-796-9845**
Phone:	(b) (6)	**Phone:**	**301-796-3908**
Pages, including cover sheet: 2		**Date:**	**January 20, 2010**

RE: Information Requests for NDA 021344

Dear Mr. Troise

Please refer to your New Drug application (NDA 021344) for FASLODEX® (fulvestrant) injection submitted on November 12, 2009. During our review of the CMC section of your submission, we have the following information requests:

Please submit an environmental assessment or a request for categorical exclusion from environmental impact analysis.

Please respond to these requests by no later than January 22, 2010 at 12:00 PM EST. Please submit an amendment to your application with your response to the requests using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) or FAX (301-796-9845) no later than January 22, 2010, at 12:00 PM EST.

Thank you.
Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
CDER, FDA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
01/20/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR STUDY ENDPOINTS CONSULTATION

TO ***(Division/Office)***:
Study Endpoints and Label Development Team (SEALD)
CDER/OND-IO White Oak Bldg 22, Mail Drop 6411

FROM ***(Division/Office)***: Alberta Davis-Warren/RPM
Division of Drug Oncology Products/Office of Oncology Drug Products/ 301-796-3908/Alberta.Davis-Warren@fda.hhs.gov

DATE OFCONSULT REQUEST	IND/NDA/BLA NO.	SERIAL NO/SUPPL. NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12-23-09	NDA 21344	SE12	Efficacy Supplement	11-12-09

NAME OF DRUG	NAME OF SPONSOR/APPLICANT	CLASSIFICATION OF DRUG	REQUESTED COMPLETION DATE
Faslodex	AstraZeneca		May 24, 2010

DRUG DEVELOPMENT PHASE (pre-IND/NDA/BLA; IND/BB-IND Phase I, II, III; NDA/BLA):

PDUFA date (if associated with NDA/BLA): September 13, 2010

MEETING DATES FOR SUBMISSION (IF APPLICABLE) several labeling meetings: May 24, June3, June 28, July 15, July 22, and July 29th 2010.

Internal: Sponsor:

MEETING TYPE (A, B, C):

STUDY ENDPOINT REVIEW (PLEASE FILL IN THE APPROPRIATE INFORMATION)

PROPOSED INDICATION:

INSTRUMENT(S) TO BE EVALUATED:

IS A COPY OF INSTRUMENT(S) TO BE REVIEWED INCLUDED IN THE SUBMISSION? IF NOT, PLEASE OBTAIN A COPY FROM THE SPONSOR/APPLICANT.

CONSULT REVIEW REQUESTED (PLEASE FILL IN A BRIEF SUMMARY OF WHAT IS BEING REQEUSTED; INCLUDE INFORMATION ON THE TYPE OF DOCUMENT BEING REVIEWED SUCH AS SPA, PEDIATRIC WR, PROTOCOL)

The purpose of this consult is to request SEALD to please review the label, this submission is a PLR converted label submitted for the first time. Tatiana Prowell is the clinical reviewer for this NDA. The submission is an efficacy supplement for NDA 21344 Faslodex. The indication is [redacted] (b) (4) The sponsor proposes to change the dosage from 250 mg to 500mg.

The efficacy supplement is in the EDR:
\\CDSESUB1\EVSPROD\NDA021344\0005

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ INTEROFFICE MAIL ☐ HAND -CARRIED ☐ E-MAIL
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
12/23/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO: **CDER-DDMAC-RPM**	FROM: (Name/Title, Office/Division/Phone number of requestor) Alberta Davis-Warren/RPM, OODP/DDOP/301-796-3908

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
12-23-09		021344	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Faslodex	Standard		July 15, 2010

NAME OF FIRM:	
AstraZeneca	PDUFA Date: September 13, 2010

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☐ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ■ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission \\CDSESUB1\EVSPROD\NDA021344\0005

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS: Please Review the label for NDA 21344 SE12. Please contact me if you have any questions. Thank you. Submission date November 12, 2009.
Mid-Cycle Meeting: [Insert Date] April 15, 2010

Labeling Meetings: [Insert Dates] May 24, June 3, June 28, July 15, and July 22, 2010

Wrap-Up Meeting: [Insert Date] July 29, 2010

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
12/23/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE

FROM: Alberta Davis-Warren RPM/OODP/DDOP
301-796-3908

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
December 9, 2009		021344	Efficacy Supplement	Novenber 12, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Faslodex	Standard		March 1, 2010

NAME OF FIRM: AstraZeneca

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- X SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The purpose of this consult is to request DRisk to review the package insert for NDA 21344. Faslodex efficacy supplement #12. This efficacy supplement provides for safety and efficacy information to support a dose change from the currently approved 250 mg dose to a 500 mg dose. It also provides for changes to the secondary packaging for the 500 mg dose and how these changes affect the CMC file, as well as the use of an additional alternate site for the secondary packaging of FASLODEX. Labeling meetings are not scheduled yet. Tatiana Prowell is the clinical reviewer for this NDA.

\\CDSESUB1\EVSPROD\NDA021344\0005

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ■ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
12/09/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM: Alberta Davis-Warren RPM/OODP/DDOP
Mail: OSE	301-796-3908

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
December 7, 2009		021344	Efficacy Supplement	Novenber 12, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Faslodex	Standard		

NAME OF FIRM: AstraZeneca

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- X SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
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IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The purpose of this consult is to request DMEPA to review the package insert, carton and container for NDA 21344. Faslodex efficacy supplement #12. This efficacy supplement provides for safety and efficacy information to support a dose change from the currently approved 250 mg dose to a 500 mg dose. It also provides for changes to the secondary packaging for the 500 mg dose and how these changes affect the CMC file, as well as the use of an additional alternate site for the secondary packaging of FASLODEX. Labeling meetings are not scheduled yet. Tatiana Prowell is the clinical reviewer for this NDA.

\\CDSESUB1\EVSPROD\NDA021344\0005

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)

	■ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
12/07/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021344/S-012 **PRIOR APPROVAL SUPPLEMENT**

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

Dear Mr. Troise:

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

Name of Drug Product:	Fulvestrant (Faslodex Injection) 250 mg/5 mL
NDA Number:	021344
Supplement number:	012
Review Priority Classification:	Standard
Date of supplement:	November 12, 2009
Date of receipt:	November 13, 2009

This supplemental application proposes the following change(s):
To provide safety and efficacy information to support a dose change from 250 mg dose to 500 mg dose. Also provides for changes to the secondary packaging for the 500 mg dose and how these changes affect the CMC file, as well as the use of an additional alternate site for the secondary packaging of FASLODEX® (fulvestrant) 250 mg/5 ml (50 mg/ml) Sterile solution for Injection

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 13, 2010 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 13, 2010.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

If you have questions, call me, at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Alberta E. Davis-Warren, B.S.
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

ALBERTA E DAVIS WARREN
11/25/2009

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Sylvia Gantt, HFD-003, 301-796-2123. WO51 Rm. 4195

FROM *(Name, Office/Division, and Phone Number of Requestor)*: Tu-Van Lambert, ONDQA, Division of Post-Marketing Assessment, 301-796-4246, WO21 Rm. 2625

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 23, 2009		21-344		November 12, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Faslodex	standard		September 1, 2010

NAME OF FIRM: AstraZeneca

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☒ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: The supplement provides for supporting a dose change from the currently approved 250 mg dose to a 500 mg dose. Changes in this supplement includes changes to section (b) (4)

OND PM Alberta Davis-Warren
Electronic submission: \\Cdsesub1\evsprod\NDA021344\0005 and amendment
PDUFA date: September 13, 2010

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Tu-Van Lambert	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21344	SUPPL-12	ASTRAZENECA PHARMACEUTICALS LP	FASLODEX (FULVESTRANT)250MG/5ML INJ

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/s/

TU-VAN L LAMBERT
11/23/2009

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 21344/012	**Action Goal:**	
St te:	13-NOV-2009	**District Goal:**	08-APR-2010
Regulatory:	13-SEP-2010		
Applicant:	ASTRAZENECA PHARMS	**Brand Name:**	FASLODEX (FULVESTRANT)250MG/5ML INJ
	1800 CONCORD PIKE	**Estab. Name:**	
	WILMINGTON, DE 198038355	**Generic Name:**	FULVESTRANT
Priority:	1S	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	150	001; SOLUTION, INJECTION; FULVESTRANT; 50MG/1ML	

Application Comment: SUPPLEMENT PROVIDES FOR A DOSE CHANGE FROM THE CURRENTLY APPROVED 250 MG DOSE TO A 500 MG DOSE; CMC CHANGES INCLUDE [redacted] (b) (4) AND ADDITIONAL SECONDARY PACKAGING [redacted] (b) (4) (on 23-NOV-2009 by T. LAMBERT () 301-796-4246)

FDA Contacts:	T. LAMBERT	Project Manager	301-796-4246
	L. ZHOU	Team Leader	301-796-1781

Overall Recommendation: ACCEPTABLE on 26-AUG-2010 by A. INYARD ()

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9610422 **FEI:** 3002850317

ASTRAZENECA UK LTD

BUSINESS PK CHARTER WAY, SK102NA
MACCLESFIELD, CHESHIRE, , UNITED KINGDOM

DMF No: (b) (4) **AADA:** I 052121

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Estab. Comment: THIS FACILITY (b) (4) SECONDARY PACKAGING (b) (4) (on 23-NOV-2009 by T. LAMBERT () 301-796-4246)

Profile: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	23-NOV-2009				LAMBERTTU
SUBMITTED TO DO	24-NOV-2009	10-Day Letter			INYARDA
DO RECOMMENDATION	24-NOV-2009			ACCEPTABLE	JOHNSONE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	25-NOV-2009			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 21344/012	**Action Goal:**	
Submitted:	13-NOV-2009	**District Goal:**	08-APR-2010
Regulatory:	13-SEP-2010		
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	WILMINGTON, DE 198038355	**Generic Name:**	FULVESTRANT
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Application Comment: SUPPLEMENT PROVIDES FOR A DOSE CHANGE FROM THE CURRENTLY APPROVED 250 MG DOSE TO A 500 MG DOSE; CMC CHANGES INCLUDE (b) (4) AND ADDITIONAL SECONDARY PACKAGING (b) (4) (on 23-NOV-2009 by T. LAMBERT () 301-796-4246)

FDA Contacts:	T. LAMBERT	Project Manager	301-796-4246
	L. ZHOU	Team Leader	301-796-1781

Overall Recommendation:

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

tablishment: **CFN:** 9610422 **FEI:** 3002850317

ASTRAZENECA UK LTD

BUSINESS PK CHARTER WAY, SK102NA
MACCLESFIELD, CHESHIRE, , UNITED KINGDOM

MF No: (b) (4) **AADA:** I 052121

sponsibilities: FINISHED DOSAGE RELEASE TESTER

tab. Comment: THIS FACILITY (b) (4) SECONDARY PACKAGING (b) (4) (on 23-NOV-2009 by T. LAMBERT () 301-796-4246)

ofile: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS **OAI Status:** NONE

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Comment				Reason	
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JBMITTED TO DO	24-NOV-2009	10-Day Letter			INYARDA
) RECOMMENDATION	24-NOV-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
) RECOMMENDATION	25-NOV-2009			ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9610422 **FEI:** 3002850317

ASTRAZENECA UK LTD

BUSINESS PK CHARTER WAY, SK102NA
MACCLESFIELD, CHESHIRE, , UNITED KINGDOM

DMF No: (b) (4) **AADA:** I 052121

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Estab. Comment: THIS FACILITY (b) (4) SECONDARY PACKAGING (b) (4)
(on 23-NOV-2009 by T. LAMBERT () 301-796-4246)

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SUBMITTED TO DO	24-NOV-2009	10-Day Letter			INYARDA
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				BASED ON FILE REVIEW	
OC RECOMMENDATION	25-NOV-2009			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

pplication:	NDA 21344/012	**Action Goal:**	
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egu	13-SEP-2010		
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DA Contacts:	T. LAMBERT	Project Manager	301-796-4246
	L. ZHOU	Team Leader	301-796-1781

verall Recommendation: