CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021344Orig1s020

Trade Name:	FASLODEX
Generic or Proper Name:	fulvestrant Injection, 250 mg/5 mL
Sponsor:	AstraZeneca Pharmaceuticals LP
Approval Date:	November 9, 2012
Change:	For updated results of overall survival data from a Randomized, 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 (D6997C00002), also known as the 'CONFIRM' study.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021344/S-019/S-020 **SUPPLEMENT APPROVAL**

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

Dear Mr. Troise:

Please refer to your Supplemental New Drug Applications (sNDAs) dated May 10, and June 28, 2012 received May 10 and June 28, 2012, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Faslodex® (fulvestrant) Injection, 250 mg/5 mL.

We acknowledge receipt of your amendments dated May 15, July 24, October 12, and October 19, 2012 (S-019).

We also acknowledge receipt of your amendments dated July 13 and July 25, 2012 (S-020).

S-019: "Changed Being Effective" supplemental new drug application S-019 provides an update for nonclinical toxicology for post-marketing safety data and information from a mouse carcinogenicity study (VKS0539 (0118CM).

S-020: "Prior Approval" efficacy supplemental new drug application S-020 provides for updated results of overall survival data from a Randomized, 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 (D6997C00002), also known as the 'CONFIRM' study.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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 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, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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 314.81(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.

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 Techiya Toaff, Regulatory Project Manager, at (301) 796-4256.

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:
Content of Labeling

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
11/09/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s020

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

----------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)
- Pediatric Patients: efficacy has not been demonstrated in girls with McCune-Albright Syndrome and progressive precocious puberty. (8.4)

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

Revised: 11/2012

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 days1, 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

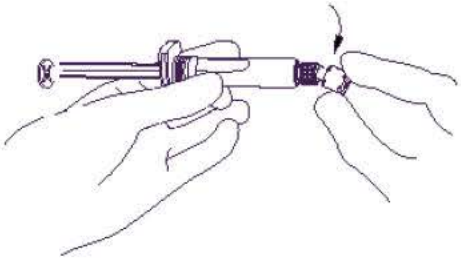


Figure 2

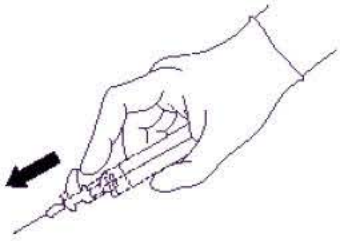
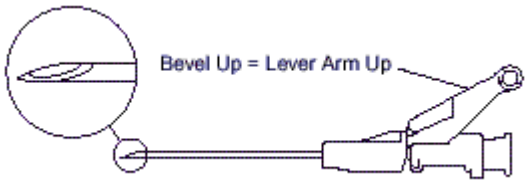


Figure 3



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.

Elevation of bilirubin, elevation of gamma GT, hepatitis, and liver failure have been reported infrequently (<1%).

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 (5.3)]*
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

A multi-center, single-arm, open-label, study of fulvestrant was conducted in 30 girls with McCune-Albright Syndrome (MAS) associated with progressive precocious puberty (PPP). The median age at informed consent was 6 years old (range: 1 to 8).

The first 10 patients initially received fulvestrant 2 mg/kg. Based on PK data from the first 6 patients, all 10 patients receiving 2 mg/kg were escalated to a dose of 4 mg/kg and all other patients received 4 mg/kg from study entry.

Baseline measurements for vaginal bleeding days, bone age, growth velocity, and Tanner staging for at least 6 months prior to study entry were provided retrospectively by the parent, guardian or local consultant. All measurements during the study period were collected prospectively. Patients' baseline characteristics included the following: a mean ± SD chronological age of 5.9 ± 1.8 years; a mean rate of bone age advancement (change in bone age in years divided by change in chronological age in years) of 2.0 ± 1.03; and a mean growth velocity z-score of 2.4 ± 3.26.

Twenty-nine of 30 patients completed the 12-month study period. The following results were observed: 35% (95% CI: 16%, 57%) of the 23 patients with baseline vaginal bleeding experienced a complete cessation of vaginal bleeding on-treatment (month 0 to 12); a reduction in the rate of bone age advancement during the 12-month study period compared to baseline (mean change = -0.9 [95% CI = -1.4, -0.4]); and a reduction in mean growth velocity Z-score on-treatment compared to baseline (mean change = -1.1 [95% CI = -2.7, 0.4]). There were no clinically meaningful changes in median Tanner stage (breast or pubic), mean uterine volume, or mean ovarian volume, or predicted adult height (PAH) on-treatment compared to baseline. The effect of Faslodex on bone mineral density in children has not been studied and is not known.

Eight patients (27%) experienced adverse reactions that were considered possibly related to Faslodex. These included injection site reactions (inflammation, pain, hematoma, pruritis, rash), abdominal pain, contusion, tachycardia, hot flush, extremity pain, and vomiting. Nine (30.0%) patients reported an SAE, none of which were considered related to Faslodex. No patients discontinued study treatment due to an AE and no patients died.

Pharmacokinetics

The pharmacokinetics of fulvestrant was characterized using a population pharmacokinetic analysis with sparse samples per patient obtained from 30 female pediatric patients aged 1 to 8 years with PPP associated with MAS. Pharmacokinetic data from 294 postmenopausal women with breast cancer who received 125 or 250 mg monthly dosing regimen were also included in the analysis.

In these pediatric patients receiving 4 mg/kg monthly intramuscular dose of fulvestrant, the geometric mean (SD) CL/F was 444 (165) mL/min which was 32% lower than adults. The geometric mean (SD) steady state trough concentration (Cmin,ss) and AUCss was 4.19 (0. 87) ng/mL and 3680 (1020) ng*hr/mL, respectively.

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

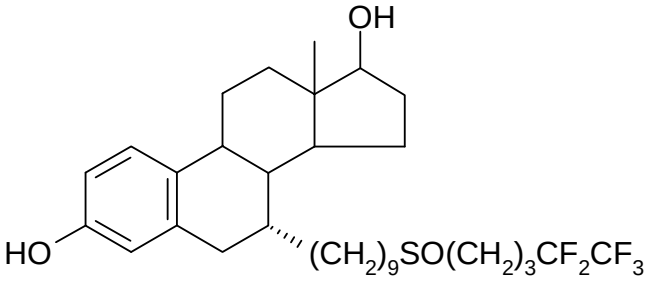
Negligible amounts of fulvestrant are eliminated in urine; therefore, a study in patients with renal impairment was not conducted. In the advanced breast cancer trials, fulvestrant concentrations in women with estimated creatinine clearance as low as 30 mL/min were similar to women with normal creatinine.

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.

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

Two-year carcinogenesis studies were conducted in rats and mice. Positive findings were observed in both species. Rats were treated 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. Mice were treated at oral doses of 0, 20, 150 and 500 mg/kg/day. These doses correspond to 0.8-, 8.4- and 18-fold (in females) and 0.8-, 7.1- and 11.9- fold (in males), the systemic exposure [$AUC_{0\text{-}30\ days}$] achieved in women receiving the recommended dose of 500 mg/month. There was an increased incidence of sex cord stromal tumors (both benign and malignant) in the ovary of mice at doses of 150 and 500 mg/kg/day. 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 55% of patients had visceral disease.

Results of Study 1 are summarized in Table 4. The efficacy of FASLODEX 500 mg was compared to that of FASLODEX 250 mg. Figure 4 shows a Kaplan-Meier plot of the Progression Free Survival (PFS) data after a minimum follow-up duration of 18 months demonstrating statistically significant superiority of FASLODEX 500 mg vs FASLODEX 250 mg. In the initial Overall Survival (OS) analysis after a minimum follow-up duration of 18 months, there was no statistically significant difference in OS between the two treatment groups. After a minimum follow-up duration of 50 months, an updated OS analysis was performed. Figure 5 shows a Kaplan-Meier plot of the updated OS data.

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] **Updated Analysis**[e] (% of patients who died)	261 (72.1%)	293 (78.3%)
Median OS (months)	26.4	22.3
Hazard Ratio[b] (95% CI[c])[f]	0.81 (0.69-0.96)	
ORR[g] (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. Minimum follow-up duration of 18 months.

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

[c]CI = Confidence Interval

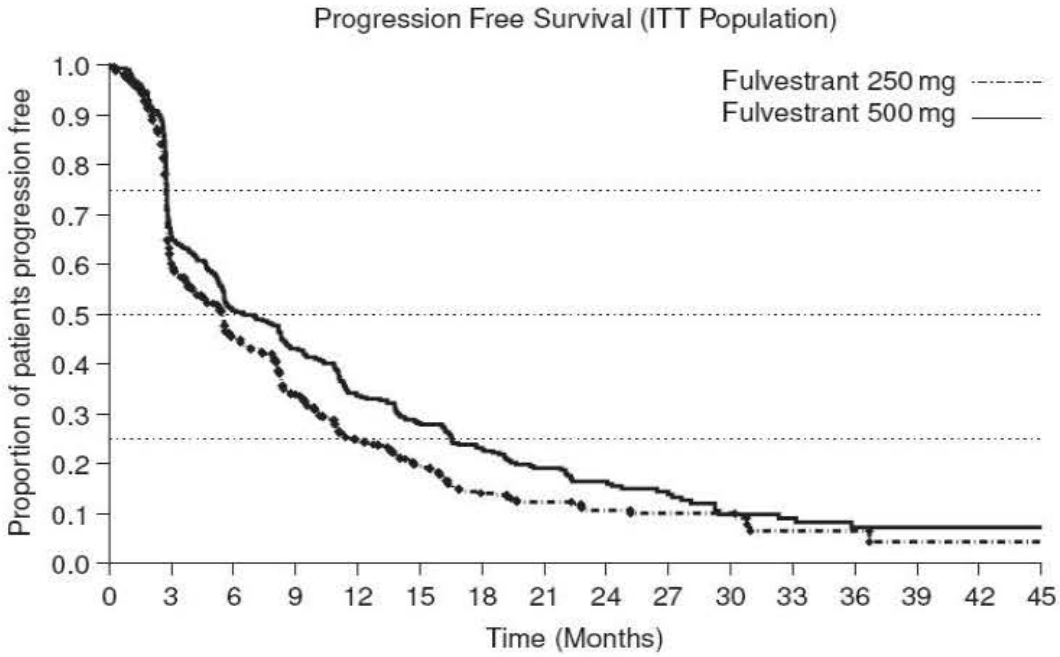
[d]OS = Overall Survival

[e]Minimum follow-up duration of 50 months.

[f]Not statistically significant as no adjustments were made for multiplicity.

[g]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). Minimum follow-up duration of 18 months.

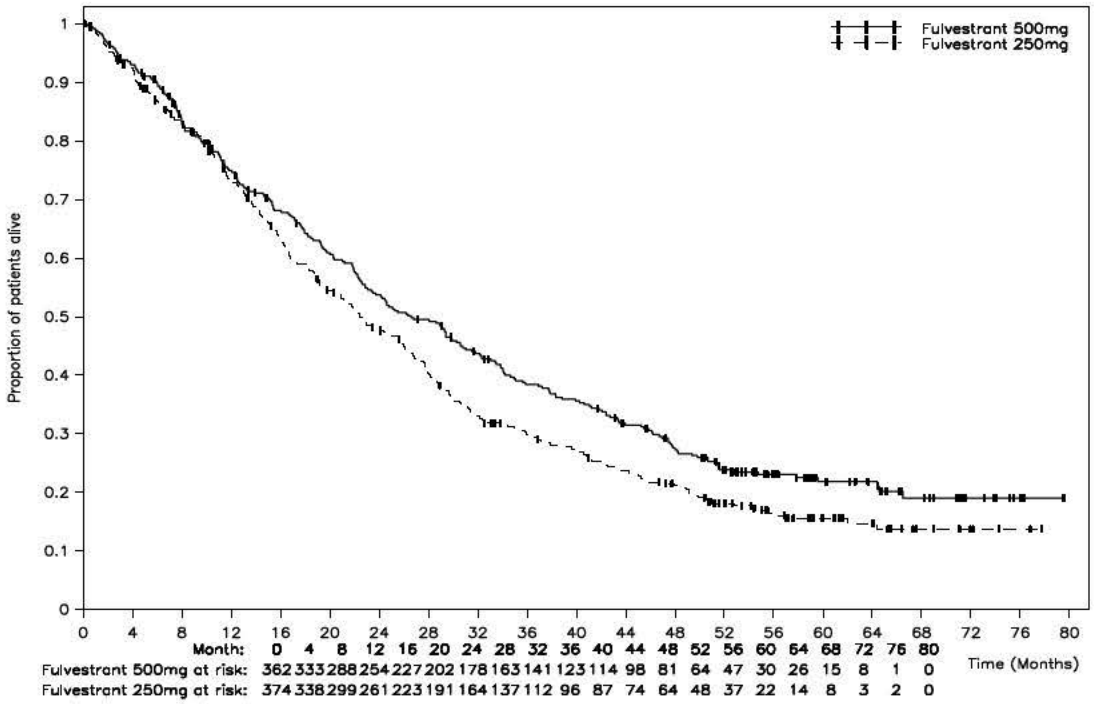
Figure 4 Kaplan-Meier PFS: Study 1 ITT Population



Number at risk

Fulvestrant 250 mg	374	218	161	119	85	66	43	33	25	13	12	4	3	1	1
Fulvestrant 500 mg	362	228	173	147	113	92	71	51	37	24	13	11	7	4	2

Figure 5 **Kaplan-Meier OS (minimum follow-up duration of 50 months): Study 1 ITT Population**



Tick marks indicate censored observations
Not statistically significant as no adjustments were made for multiplicity

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]) 2-sided 95.4% CI[e]	0.0 (-6.3, 8.9)		5.4 (-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 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

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

Rev. 11/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s020

OFFICER/EMPLOYEE LIST

Employee List

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RPM: Techiya Toaff

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s020

MEDICAL REVIEW(S)

Addendum to Clinical Review	
NDA	21344
Submission Date:	June 28, 2012
Brand Name:	Faslodex®
Generic Name:	Fulvestrant
Formulation:	500 mg IM injection
Clinical and Statistical Reviewers:	Tatiana Prowell, M.D. Somesh Chattopadhyay, Ph.D.
Clinical and Statistical Team Leaders:	Amy McKee, M.D. Shenghui Tang, Ph.D.
Sponsor:	AstraZeneca
Submission Type;	sNDA 21344/eCTD seq #68
Dosing regimen:	500 mg IM on d#1, 15, (b) (4) monthly thereafter
Indication:	(b) (4)

Executive Summary

The purpose of this addendum is to note that there is a difference between the median OS in FDA's review and the applicant's reported results due to rounding off of dividing constant to convert the number of days to the number of months. The application reported the median OS as 26.4 months in the Faslodex 500 mg arm whereas the number is 26.5 months in the FDA's review. The number of days was divided by 30.4375 in the applicant's calculation and by 30.4 in FDA's calculation to obtain the number of months.

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

/s/

SOMESH CHATTOPADHYAY
11/08/2012

SHENGHUI TANG
11/08/2012

Clinical Review	
NDA	21344
Submission Date:	June 28, 2012
PDUFA Goal Date:	December 28, 2012
Review Submitted:	November 1, 2012
Brand Name:	Faslodex®
Generic Name:	Fulvestrant
Formulation:	500 mg IM injection
Clinical and Statistical Reviewers:	Tatiana M. Prowell, M.D. Somesh Chattopadhyay, Ph.D.
Clinical and Statistical Team Leaders:	Amy McKee, M.D. Shenghui Tang, Ph.D.
Sponsor:	AstraZeneca
Submission Type:	Efficacy labeling supplement sNDA 21344/eCTD seq #68
Dosing regimen:	500 mg IM on d#1, 15, (b) (4) monthly thereafter
Indication:	(b) (4) with disease progression following anti-estrogen therapy

Executive Summary

Faslodex (fulvestrant) is a pure estrogen receptor antagonist administered via intramuscular injection. The current submission (eCTD sequence 68) provides updated overall survival (OS) data from the CONFIRM trial (trial D6997C00002) that served as the basis for approval in September 2010 of the Faslodex 500 mg dose/schedule.

A total of 736 postmenopausal women with advanced hormone receptor-positive breast cancer and disease progression following anti-estrogen therapy were enrolled and randomized on the CONFIRM trial. Disease progression following anti-estrogen therapy was defined as recurrence while on, or within 12 months of completion of, adjuvant endocrine therapy, or progression on first-line endocrine therapy in the advanced setting. There were 362 patients randomized to the experimental arm (fulvestrant 500 mg IM on d#1, 15, 29, and monthly thereafter) and 374 patients randomized to the control arm (fulvestrant 250 mg IM monthly plus placebo). The primary endpoint was progression-free survival (PFS) by investigator assessment. A formal analysis of OS using an unadjusted log-rank test in the ITT population was planned when ≥ 50% of patients had died.

The fulvestrant 500 mg regimen was approved on the basis of a statistically significant improvement in PFS (HR 0.80; 95% CI 0.68, 0.94; p=0.006) in the CONFIRM trial with no difference in the rate of adverse events between the two arms. The OS results were supportive.

In the initial OS analysis with a minimum follow-up duration of 18 months, 378 out of 736 patients (51%) had died. There was a non-statistically significant 2.3 month difference in OS (25.1 months vs. 22.8 months) between the two treatment groups (HR=0.84; 95% CI 0.69, 1.03; log-rank p=0.09).

Following the positive results of the CONFIRM trial and FDA approval, participants were permitted to cross over to the 500 mg arm; however, only 8 patients (1.1%) elected to do so.

An updated OS analysis was performed when 75% of participants had died. With a minimum follow-up of 50 months, the median OS was 26.4 months in the fulvestrant 500 mg arm compared with 22.3 months in the fulvestrant 250 mg arm (HR 0.81; 95% CI 0.69, 0.96; p_{unadj}=0.016). Note that the p-value for the updated OS analysis is not interpretable because no adjustment of type-I error has been made for multiple OS analyses.

FDA's analysis of the sponsor's datasets confirmed the results. Figure 1 contains a Kaplan-Meier plot of the updated OS results, and Table 1 presents the updated OS data in tabular form.

Figure 1: Updated Overall Survival, Kaplan-Meier Curve

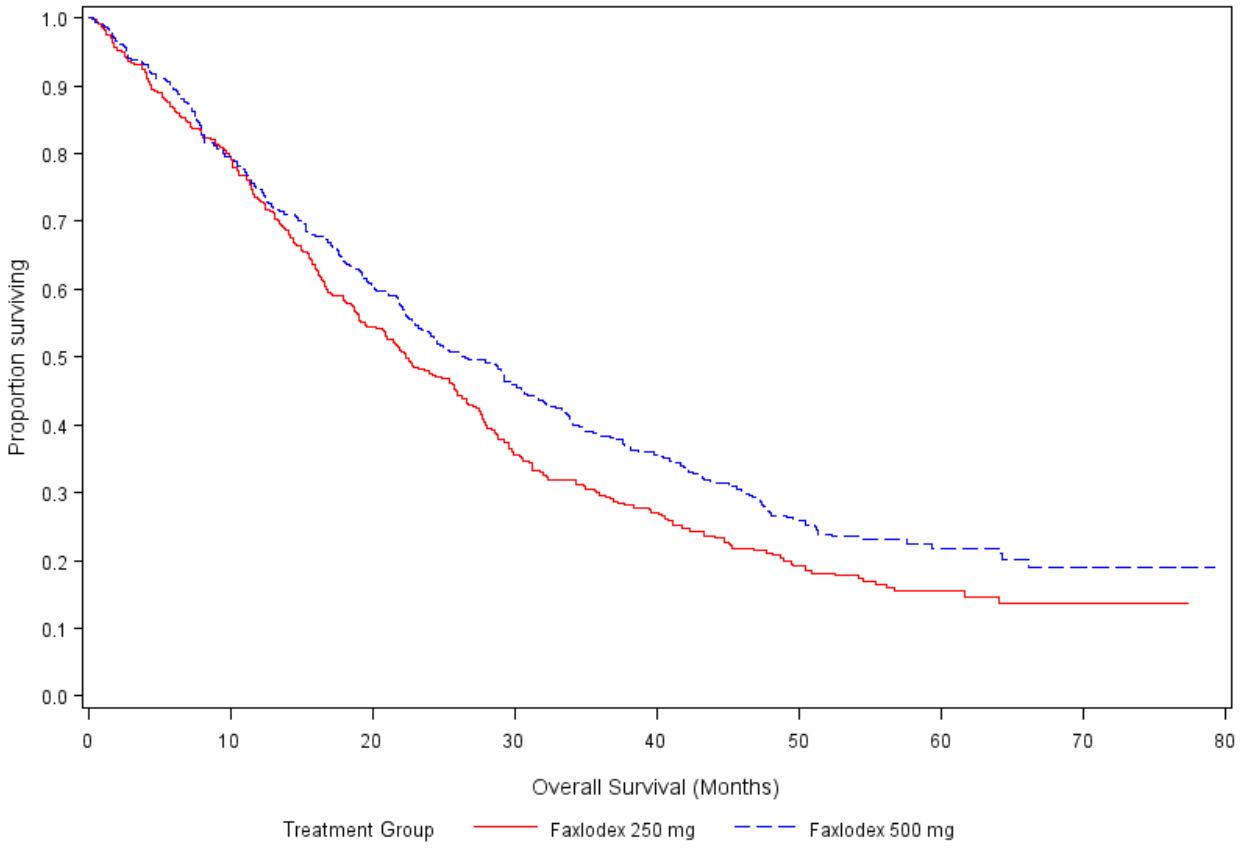


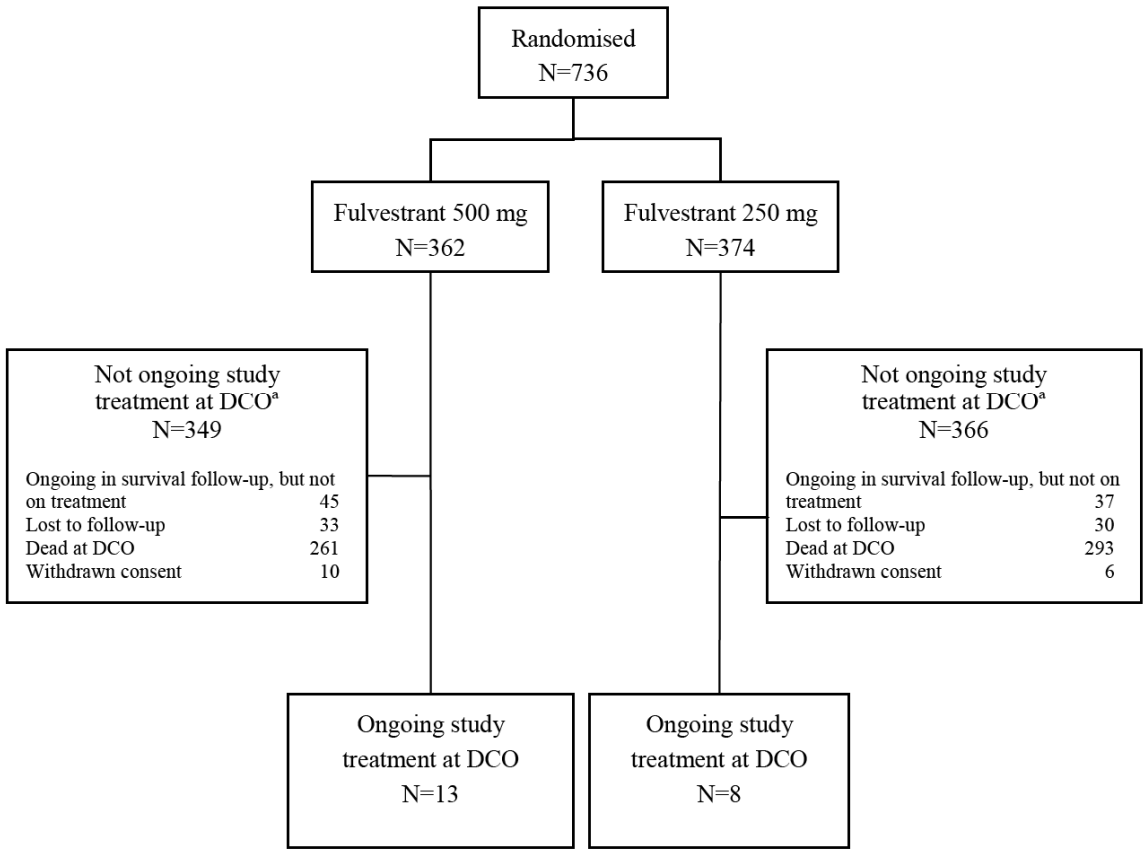
Table 1: Updated Analysis of Overall Survival

Arm	No. of Patients	Deaths n (%)	Median OS, Mos[1] (95% CI)	Hazard Ratio[2] (95%CI)	p-value[3]
Faslodex 500 mg	362	261 (72.1%)	26.5 (22.8,30.7)	0.815 (0.689, 0.963)	0.0162
Faslodex 250 mg	374	293 (78.3%)	22.3 (19.1,26.0)		

[1]Kaplan-Meier estimate
[2]Based on Cox model
[3]Based on two-sided log-rank test. Note: no adjustment of type I error rate was made for multiple OS analyses.

At the time of the data cutoff for the updated OS analysis, fewer patients had died in the fulvestrant 500 mg arm (n=261, 74.7%) than in the fulvestrant 250 mg arm (n=293, 80.0%). There were 21 patients still on treatment, 13 on the 500 mg fulvestrant arm and 8 on the 250 mg fulvestrant arm. The patient disposition at final analysis is shown below in Figure 2 below from the Sponsor:

Figure 2 Patient disposition



The reasons for discontinuation of study treatment are shown in the Sponsor's Table 2 below. The most common reason for treatment discontinuation was disease progression, which was more common in the fulvestrant 250 mg group (79.4%) than in the fulvestrant 500 mg group (76.8%). Deaths on treatment occurred less commonly in the fulvestrant 500 mg arm (2.2%) than in the fulvestrant 250 mg arm (3.7%).

Table 2 Summary of reason for discontinuation of study treatment: Full Analysis Set

Reason for discontinuation of study treatment	Number (%) of patients			
	Fulvestrant 500 mg N=362		Fulvestrant 250 mg N=374	
Eligibility criteria not fulfilled	4	(1.1)	4	(1.1)
Protocol non-compliance	2	(0.6)	2	(0.5)
Death	8	(2.2)	14	(3.7)
Adverse event	8	(2.2)	6	(1.6)
Objective progression of disease	278	(76.8)	297	(79.4)
Significant concurrent illness	1	(0.3)	0	
Patient not willing to continue treatment	6	(1.7)	5	(1.3)
Patient not willing to continue study	14	(3.9)	11	(2.9)
Patient lost to follow-up	3	(0.8)	1	(0.3)
Other	23	(6.4)	25	(6.7)

A subgroup analysis of OS by prior therapy demonstrated a greater difference in median OS between treatment arms for patients whose last endocrine therapy was tamoxifen (30.6 months versus 23.9 months; HR 0.79; 95% CI 0.63, 0.99). For patients whose last endocrine therapy was an aromatase inhibitor, the median OS results also favored the fulvestrant 500 mg arm, although the difference between arms was smaller (24.1 months versus 20.8 months; HR 0.86, 95% CI 0.67, 1.11).

In summary, the updated OS results from the CONFIRM trial demonstrate a non-statistically significant 4.1 month difference in median OS favoring the fulvestrant 500 mg arm and no new safety signals. These updated OS results should replace the existing OS results in the fulvestrant package insert. Of note, no adjustment has been made for multiplicity, and thus the 95% CI should be included in the labeling with a notation that the results are unadjusted for multiplicity and the p-value is thus not interpretable.

Recommendations

The updated OS results should be incorporated in into the Faslodex label in lieu of the previous OS results.

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

/s/

TANYA M PROWELL
11/01/2012

AMY E MCKEE
11/02/2012

SOMESH CHATTOPADHYAY
11/02/2012

SHENGHUI TANG
11/02/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s020

PHARMACOLOGY REVIEW(S)

S-019

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
Supporting document/s:	673
Applicant's letter date:	5/10/2012
CDER stamp date:	5/10/2012
Product:	Faslodex® (fulvestrant)
Indication:	Hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy.
Applicant:	AstraZeneca
Review Division:	DHOT
	(DOP1)
Reviewer:	Kimberly Ringgold, PhD
Acting Team Leader:	Todd Palmby, PhD
Division Director:	John Leighton, PhD, DABT (Acting)
	(Robert Justice, MD)
Project Manager:	Kim Robertson

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Nonclinical studies, including a rat carcinogenicity study, were reviewed under the original approval by Lilliam Rosario, PhD in 2002. In this current submission, the Applicant has submitted the final report from a mouse carcinogenicity study. The design of the study was acceptable and based on previous toxicology studies and/or the guidance of the Executive Carcinogenicity Assessment Committee (ECAC).

Mutagenic/Genotoxic: No. Fulvestrant was not mutagenic in an *in vitro* bacterial reverse mutation assay (Ames), and was not genotoxic *in vitro* in a cytogentics study in human lymphocytes or in a mammalian cell mutation assay in mouse lymphoma cells or *in vivo* in a micronucleus test in rats.

Previous Rat Carcinogenicity Study Results: The report for a 2-year carcinogenicity study in rats was submitted with the original NDA and reviewed by Dr. Lilliam Rosario with ECAC concurrence. The recommendations and conclusions were:

1) Fulvestrant increases the incidence of ovarian granulosa cell tumors in female rats, and the incidence of interstitial Leydig cell tumors in male rats.
2) The increased incidence of granulosa and Leydig cell tumors should be included in the product labeling for fulvestrant.
3) The Committee recommended that the Sponsor be asked to perform ^{32}P post-labeling study to determine if fulvestrant and/or its' metabolites may form adducts with cellular DNA.

The following is excerpted from Dr. Rosario's review:

> "Evaluation of tumor findings:
> Administration of ICI 182,780 resulted in changes in the incidence (increased and decreased) of both neoplastic and non-neoplastic findings. Several of the changes in the ovaries, uterus, mammary glands, pituitary gland, and testes are considered to be related to the pharmacological activity of ICI 182,780.
>
> ICI 182.780 increases the incidence of ovarian granulosa cell tumors and testicular interstitial Leydig cell ademomas.
>
> Ovaries: An increase in the incidence (14%) of ovarian granulosa cell tumors was recorded in the high dose female animals (7/50 rats at 10 mg/rat/15d). This was also associated with an increased incidence of hyperplasia of follicular granulosa cells in these animals. Also in the ovaries, there was an increase incidence of abnormal follicular

development and a reduction in sertoliform tubular hyperplasia. Spontaneous incidence of granulosa cell tumors for this strain of rat is 0.06% (n=1729) (Giknis and Clifford, 2001 (b) (4)). The conducting laboratory reports background instances varying from 0/120 to 1/120 (0.2%). Another study (n= 4493) with the same strain and source reports 0.3% (Gregson and Abbott, 1984).

Testes: There was an increase (2-12%) incidence of interstitial Leydig cell tumors (adenomas) in drug-treated animals. These tumors were present at a low incidence (4%) in the saline control group and absent in the vehicle control groups. The incidence in the high dose group was similar to controls (2%) while increased (8-12%) in the two lower dose groups. Spontaneous incidence for this tumor in this strain of rat is 2.35%."

MOUSE CARCINOGENICITY STUDY: Standard two-year bioassay

Mouse Study Duration (weeks):	104
Study Starting Date:	April 24, 2008
Study Ending Date:	March 16, 2011
Mouse Strain:	Crl:CD1(ICR)
Route:	Oral gavage
Dosing Comment:	None

Number of Mice – Toxicology Groups (see study review for more details):

- Water control: 57 M / 57 F
- Vehicle control (1): 57 M / 57 F
- Vehicle control (2): 57 M / 57 F
- Low Dose: 57 M / 57 F
- Mid Dose: 57 M / 57 F
- High Dose: 57 M / 57 F

Mouse Dose Levels:

- Low Dose: 20 mg/kg/day
- Mid Dose: 150 mg/kg/day
- High Dose: 500 mg/kg/day

Basis for Dose Selection:

The 500 mg/kg high dose selection was based on a 25-fold multiplicity of anticipated monthly exposure (AUC) in the mouse vs. AUC in women at the approved 250 mg/month dose, and in part on the tolerability of the vehicle formulation. The ECAC concurred with the 20 mg/kg low dose but recommended a mid dose of 150 mg/kg. In addition, the Sponsor stated that due to the (b) (4)

Prior FDA Dose Concurrence:
Yes (see Appendix A). In a meeting with the ECAC on February 12, 2008, the Division of Metabolism and Endocrinology Products (DMEP) and members of the ECAC concurred with the low and high dose selections of 20 and 500 mg/kg/day, respectively, based on an expected 25-fold ratio of AUC exposure at 500 mg/kg/day compared to AUC values in women administered monthly intramuscular injections of 250 mg fulvestrant. The ECAC recommended a mid dose of 150 mg/kg/day, (b) (4) the Applicant followed the ECAC's recommendation for mid dose selection.

1.2 Brief Discussion of Nonclinical Findings

Mouse Carcinogenicity:
Positive; study results indicate that fulvestrant is carcinogenic in female mice.

Mouse Tumor Findings:
The CDER statistical reviewer indicated that there was a statistically significant, dose-dependent increase in benign and malignant granulosa cell tumors (150 & 500 mg/kg: $p < 0.001$), benign luteomas (150 & 500 mg/kg: $p < 0.001$), benign sex cord stromal tumors (150 mg/kg: $p = 0.012$; 500 mg/kg: $p < 0.001$), and tubulostromal adenomas (150 mg/kg: $p < 0.001$; 500 mg/kg: $p = 0.011$) in the ovaries in female mice. A pair-wise relationship in females between the 150 and 500 mg/kg groups and the control (water or vehicle) groups was also statistically significant for these findings. There were no statistically significant neoplastic findings in male mice.

Neoplastic Finding	Incidence				P-value			
Dose (mg/kg)	VC	20 Low	150 Mid	500 High	Dose-response	VC vs. L	VC vs. M	VC vs. H
Benign granulosa cell tumor	2	3	13	10	<0.001	0.1742	<0.001	<0.001
Benign luteoma	0	2	16	11	<0.001	0.0968	<0.001	<0.001
Malignant granulosa cell tumor	0	2	12	9	<0.001	0.0933	<0.001	<0.001
Benign sex cord stromal tumor	3	2	7	12	<0.001	0.4909	0.0119	<0.001
Tubulostromal adenoma	0	0	6	4	.0085	-	<0.001	0.0108

VC: vehicle control; -: no change

1.3 Recommendations

1.3.1 Approvability

The Pharmacology/Toxicology review supports approval of the revised package insert to include results from the mouse carcinogenicity study.

1.3.3 Labeling

Section 13.1 in the current FDA approved package insert for Faslodex is as follows:

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.

The revised version of section 13.1 for the Faslodex package insert to incorporate the results of the mouse carcinogenicity study following negotiation with the Applicant is as follows:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenesis studies were conducted in rats and mice. Positive findings were observed in both species. Rats were treated 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. Mice were treated at oral doses of 20, 150 and 500 mg/kg/day. These doses correspond to 0.8-, 8.4- and 18-fold (in females) and 0.8-, 7.1- and 11.9–fold (in males) the systemic exposure [$AUC_{0\text{-}30\ days}$] achieved in women receiving the recommended dose of 500 mg/month. There was an increased incidence of sex cord stromal tumors (both benign and malignant) in the ovary of mice at doses of 150 and 500 mg/kg/day. 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_{0-30} days] achieved in women receiving the recommended dose of 500 mg/month.

Rationale:

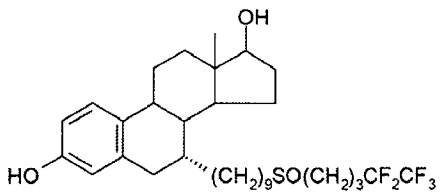
The recommended changes are to add the relevant information from the study report for the mouse carcinogenicity study and to combine these results with the findings in the rat carcinogenicity study reported in the approved Faslodex package insert.

---

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:

NDA 21344

2.3 Clinical Formulation

2.3.1 Drug Formulation

FASLODEX is supplied in sterile single patient pre-filled syringes containing 50-mg/mL fulvestrant either as a single 5 mL or two concurrent 2.5 mL injections to deliver the required monthly dose. FASLODEX is administered as an intramuscular injection of 500 mg once monthly. Each injection 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

2.3.2 Comments on Novel Excipients: none

2.3.3 Comments on Impurities/Degradants of Concern: none

2.4 Proposed Clinical Population and Dosing Regimen

FASLODEX is indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. Faslodex 500 mg is administered intramuscularly into the buttocks slowly as two 5 mL injections, one in each buttock, on days 1, 15, 29 and once monthly thereafter.

2.5 Regulatory Background

Faslodex was approved in 2002.

8 Carcinogenicity

Study title: Fulvestrant: Carcinogenicity Study by Oral Gavage administration to CD-1 Mice for 104 Weeks

Study no.:	VKS0539 (b) (4) 0118CM (AstraZeneca)
Study report location:	eCTD 4.2.3.4.2.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	4/9/2008
GLP compliance:	Statement included and signed
QA statement:	Statement included and signed
Drug, lot #, and % purity:	(b) (4)
ECAC concurrence:	Yes (Exec. CAC meeting of 2/13/2008)

Key Study Findings

Neoplastic findings:

- Females: benign and malignant granulosa cell tumors, benign luteomas, benign sex cord stromal tumors, and tubulostromal adenomas in the ovary

Non-neoplastic findings:

- increased body weight gain in males and females
- increases in macrophage aggregates observed in the mesenteric lymph nodes
- increases in atrophy of the female reproductive tract

Adequacy of carcinogenicity study and Appropriateness of test models:

CD-1 mice are a standard rodent model used for carcinogenicity studies. The study protocol was reviewed by the ECAC, which concurred with the 500 mg/kg dose as a top dose based on an expected 25-fold ratio of AUC exposure compared to women administered monthly intramuscular injections of 250 mg fulvestrant. Subsequent to the review of the protocol for this study and the ECAC's concurrence, the recommended clinical dose of fulvestrant in the FDA approved package insert was changed to 500 mg/month based on new clinical data. Although the AUC ratio in mice compared to humans receiving 500 mg/month did not reach 25-fold, the study was acceptable based on the following: 1) study was positive for tumor findings at the mid and high dose levels; 2) the 25-fold exposure multiple was based on a previously approved clinical dose of 250 mg/month; 3) actual $AUC_{0\text{-}30\ days}$ exposure ratio in female mice that received the high dose level of 500 mg/kg/day compared to humans was 18-fold. Animal survival was 32% in males and 37% in females, which was adequate for the assessment of tumorigenic potential.

Methods

Doses:	0, 20, 150, & 500 mg/kg/day
Frequency of dosing:	once daily for at least 104 weeks
Dose volume:	10 mL/kg
Route of administration:	Oral, by gavage
Formulation/Vehicle:	Imwitor 988 43.11% w/w, Cremophor RH40 29.56% w/w, Miglyol 812-N 14.00% w/w, Ethanol 13.33% w/w; Vehicle control: 1:2 dilution with water
Basis of dose selection:	Based on data from 13 week toxicity study and ECAC concurrence 2/3/2008
Species/Strain:	CD-1 Mouse
Number/Sex/Group:	57 - 62
Age:	35 – 41 days
Animal housing:	Individual
Paradigm for dietary restriction:	As lib food and water
Dual control employed:	Yes
Interim sacrifice:	No
Satellite groups:	Yes (see table 1)

Group	Animals	Animal numbers	Treatment	Daily dose levels mg/kg/day #
Main study groups				
1	57M + 57F	1-57, 451-507	Water Control	0
2	57M + 57F	85-141, 535-591	Vehicle Control	0
3	57M + 57F	142-198, 592-648	Vehicle Control	0
4	57M + 57F	199-255, 649-705	Fulvestrant	20
5	57M + 57F	283-339, 733-789	Fulvestrant	150
6	57M + 57F	367-423, 817-873	Fulvestrant	500
Satellite groups: Toxicokinetics†				
1	27M + 27F	58-84, 508-534	Water Control	0
4	27M + 27F	256-282, 706-732	Fulvestrant	20
5	27M + 27F	340-366, 790-816	Fulvestrant	150
6	27M + 27F	424-450, 874-900	Fulvestrant	500
Cohort groups@				
1	5F	946-950	Water Control	0
6	5F	951-955	Fulvestrant	500

Expressed in terms of the test substance as supplied.
† Satellite animals used for planned Toxicokinetic sampling only. Refer to Table 4 and Appendix F for actual numbers sampled.
@ These animals were added to the study to replace animals that died due to accidental misdosing during Week 1 of the study. Start of treatment and necropsy were 6 weeks after the rest of the study.

(excerpted from Sponsor's report)

Observations and Results

Mortality

Table 1: Mortality Table

Group/Sex	1M	2M	3M	4M	5M	6M	1F	2F	3F	4F	5F	6F
Dose (mg/kg/day)	0	0	0	20	150	500	0	0	0	20	150	500
Main and Cohort studies												
Found dead	11	11	8	8	16	7	12	5	8	8	7	16
Killed for welfare reasons	25	22	18	30	23	29	23	31	26	26	26	19
Mortality	36	33	26	38	39	36	35†	36†	34	34	33	35†
No. of survivors	21	24	31	19	18	21	27	21	23	23	24	27
% survival	37	42	54	33	32	37	44	37	40	40	42	44

† Includes mice killed by misdosing in Week 1 (Group 1, 2; Group 2, 1; Group 6, 6)

(excerpted from Sponsor's report)

Summary: No drug-related effects on survival in any groups compared to controls.

Cause of Death Findings:

	No. of Males affected					
Sex	1M	2M	3M	4M	5M	6M
Dose (mg/kg)	0 WC	0 VC	0 VC	20	150	500
No. of animals	57	57	57	57	57	57
Lymphoma NOS	5	6	10	3	4	3
	No. of Females affected					
Sex	1F	2F	3F	4F	5F	6F
Dose (mg/kg)	0 WC	0 VC	0 VC	20	150	500
No. of animals	62	57	57	57	57	62
Lymphoma NOS	12	22	22	21	10	21
Malignant granulosa cell tumor	-	-	-	-	11	1

WC: water control; VC: vehicle control; -: no change

Clinical signs

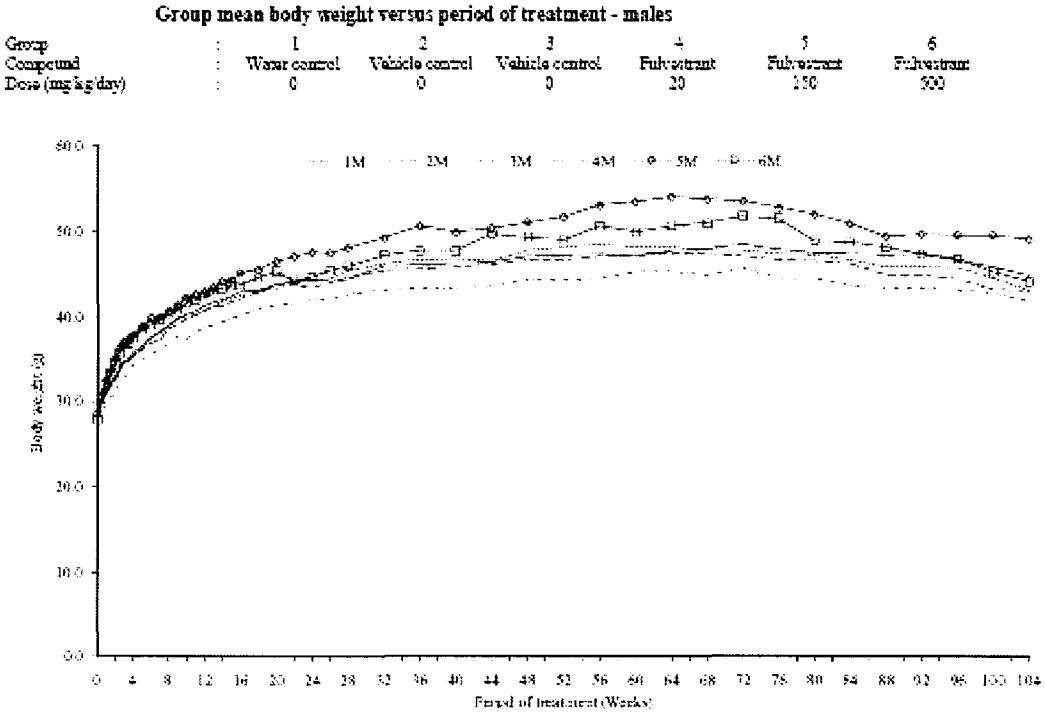
	No. of Males affected					
Sex	1M	2M	3M	4M	5M	6M
Dose (mg/kg)	0 WC	0 VC	0 VC	20	150	500

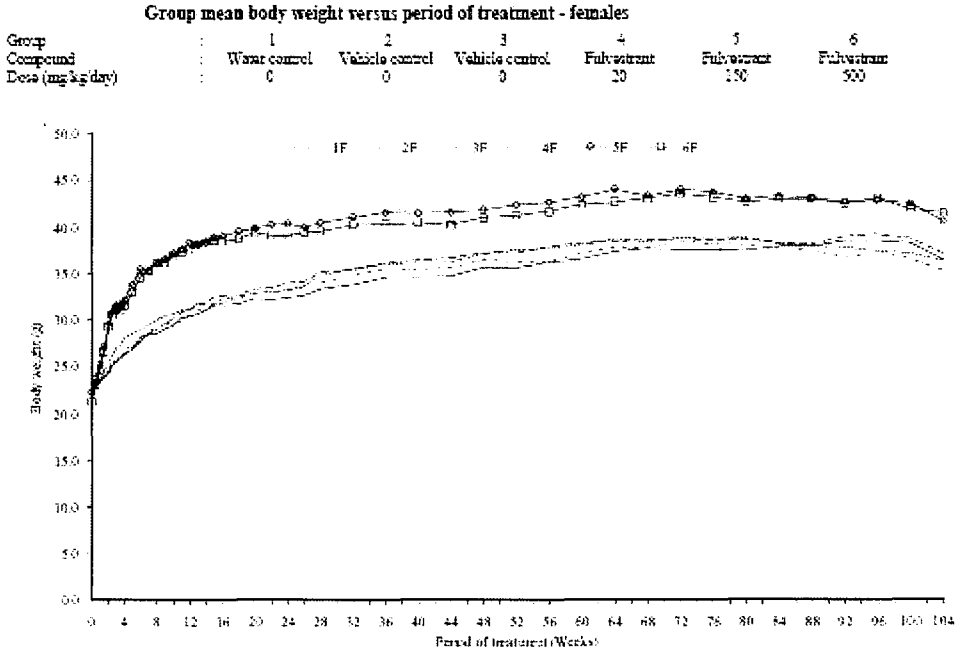
No. of animals	57	57	57	57	57	57
Salivation	-	-	-	-	1	1
Dull eyes	-	-	-	-	-	1
Swollen upper eyelid	-	-	-	-	-	2
Swollen lower eyelid	-	-	-	-	-	1
Eyes partially closed	-	-	-	-	-	1
Abnormal gait	-	-	-	-	1	2
Limited use of limbs	-	-	-	-	-	1
	No. of Females affected					
Sex	1F	2F	3F	4F	5F	6F
Dose (mg/kg)	0 WC	0 VC	0 VC	20	150	500
No. of animals	62	57	57	57	57	62
Repetitive movement	-	-	-	-	-	1
Salivation	-	-	-	-	-	1
Green feces	-	-	-	-	1	1
Swaying	-	-	-	-	-	2
Posture (tilted to right)	-	-	-	-	1	1

WC: water control; VC: vehicle control; -: no change

Papable Swellings: Unremarkable

Body Weights: *(graphs excerpted from sponsor's report)*





Summary: There was an increase in bodyweight gain in the 150 and 500 mg/kg in males and females.

Feed Consumption: Unremarkable

Ophthalmology: Unremarkable

Hematology: Unremarkable

Gross Pathology

Macroscopic finding		No. of Males affected					
Sex		1M	2M	3M	4M	5M	6M
Dose (mg/kg)		0 WC	0 VC	0 VC	20	150	500
Seminal Vesicles	discolored	4	3	4	7	15	17
Preputial gland	Cystic enlargement	4	3	2	2	7	7
Testes	Blue	0	0	1	7	6	18
	Dark	0	1	2	9	12	14
	flaccid	1	1	2	12	17	11
	Prominent tubules	5	5	4	15	18	16
	Small	0	0	2	10	20	15
	Unilaterally small	1	1	2	4	4	3
		No. of Females affected					
Sex		1F	2F	3F	4F	5F	6F

Dose (mg/kg)		0 WC	0 VC	0 VC	20	150	500
Preputial gland	Cystic enlargement	-	-	1	3	16	20
Ovaries	Dark follicles	-	-	-	8	9	11

WC: water control; VC: vehicle control; -: no change

Histopathology

Peer Review: Yes, statement included and signed. A peer review of pathology findings was conducted at the test site in accordance with the SOPs of GSA (b) (4) A consensus opinion between study pathologist and peer review pathologist was achieved.

Neoplastic findings:
NOTE: A statistical review was conducted by Dr. Mohammad Atiar Rahman in the Office of Biostatistics/CDER.

Microscopic finding		No. of Males affected					
Sex		1M	2M	3M	4M	5M	6M
Dose (mg/kg)		0 WC	0 VC	0 VC	20	150	500
Kidney	Tubular cell adenoma	-	-	-	1	1	1
Pituitary	Adenoma of the par distalis	-	-	-	-	1	1
Liver	Hepatocellular carcinoma	2	3	4	4	5	5
Seminal vesicles	Adenocarcinoma	-	-	-	-	1	1
Epididymides	Rhabdomyosarcoma	-	-	-	-	-	1
Skin/subcutis	Malignant fibrous histiocytoma	2	-	-	5	1	-
		No. of Females affected					
Sex		1F	2F	3F	4F	5F	6F
Dose (mg/kg)		0 WC	0 VC	0 VC	20	150	500
Ovaries	Sex cord stromal tumor (benign)	-	2	1	2	7	12
	Sex cord stromal tumor (malignant)	-	-	-	-	-	1
	Granulosa cell tumor (benign)	1	2	-	3	13	10
	Granulosa cell tumor (malignant)	-	-	-	2	12	9
	Benign luteoma	-	-	-	2	16	11
	Tubulostromal adenoma	-	-	-	-	6	4
	Hemangioma	-	-	-	3	1	-

WC: water control; VC: vehicle control; -: no change

Statistical Analysis (provided by Dr. Rahman):

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pair-wise Comparisons

Sex	Organ Name	Tumor Name	Vehicle Cont	20 mg Low	150 mg Med	500 mg High	P-Value Dose Resp	VC vs L	VC vs M	VC vs H
Male	SKIN/SUBCUTIS	Malignant Fibrous Histiocytoma	0	5	1	0	0.8494	0.0028*	0.3333	.
Female	ADRENAL GLANDS	Subcapsular Cell Adenoma	1	2	4	1	0.4673	0.2245	0.0357*	0.5538
	LUNG	Alveolar/bronchiolar carcinoma	3	1	2	5	0.0259	0.7837	0.5027	0.0782
	OVARIES	Benign granulosa cell tumor	2	3	13	10	<0.001*	0.1742	<0.001*	<0.001*
		Benign luteoma	0	2	16	11	<0.001*	0.0968	<0.001*	<0.001*
		Hemangioma	0	3	1	0	0.7007	0.0277*	0.3140	.
		Malignant granulosa cell tumor	0	2	12	9	<0.001*	0.0933	<0.001*	<0.001*
		Sex Cord Stromal Tumor Benign	3	2	7	12	<0.001*	0.4909	0.0119	<0.001*
		Tubulostromal adenoma	0	0	6	4	0.0085*	.	<0.001*	0.0108*

Significant Findings Using Water Control and Treated Groups

Sex	Organ Name	Tumor Name	Water Cont	20 mg Low	150 mg Med	500 mg High	P-Value Dose Resp	WC vs L	WC vs M	WC vs H
Female	LIVER	Hepatocellular adenoma	0	0	3	3	0.0436*	.	0.1071	0.1160
	OVARIES	Benign granulosa cell tumor	1	3	13	10	0.0082*	0.2707	<0.001*	0.0036*
		Benign luteoma	2	2	16	11	0.0073*	0.6534	<0.001*	0.0076*
		Malignant granulosa cell tumor	0	2	12	9	0.0048*	0.2162	<0.001*	0.0012*
		Sex Cord Stromal Tumor Benign	0	2	7	12	<0.001*	0.2162	0.0044*	<0.001*
		Tubulostromal adenoma	0	0	6	4	0.0322*	.	0.0092*	0.0551

Comparison of Water and Pooled Vehicle control groups

Male No statistically significant difference in any of the observed tumor type

Female No statistically significant difference in any of the observed tumor type

Non-neoplastic findings:

Macroscopic finding		No. of Males affected					
Sex		1M	2M	3M	4M	5M	6M
Dose (mg/kg)		0 WC	0 VC	0 VC	20	150	500
Lymph node, mesenteric	↑ macrophage aggregates	1	-	-	3	36	42
	Lymphoid hyperplasia	1	-	-	1	4	4
Epididymides	↓ spermatozoa	7	8	12	33	52	43
Testis	Seminferous tubular degeneration	20	20	28	45	58	54
	Rete dilatation	2	-	3	3	-	13
Coagulating gland	Distention	9	10	8	19	31	24
	Inflammatory cell infiltration	11	7	5	17	30	20
		No. of Females affected					
Sex		1F	2F	3F	4F	5F	6F
Dose (mg/kg)		0 WC	0 VC	0 VC	20	150	500
Lymph node, mesenteric	↑ macrophage aggregates	2	-	1	6	31	40
Ovaries	Tubulostromal hyperplasia	1	1	-	2	5	3
	Hemorrhagic follicles, macrophage aggregates, pigment, atrophy	-	1	1	42	55	56
Vagina	Atrophy	4	2	1	37	47	46
Uterus	Atrophy	1	-	-	47	54	57

WC: water control; VC: vehicle control; -: no change

Summary: Increases in macrophage aggregates were observed in the lymph nodes of male and female rats. Other findings are consistent with the pharmacology of fulvestrant.

Evaluation of Tumor Findings:

There was a statistically significant, dose-dependent increase in benign and malignant granulosa cell tumors, benign luteomas, benign sex cord stromal tumors, and tubulostromal adenomas in the ovary. A pair-wise relationship between the 150 and 500 mg/kg groups and the control (water or vehicle) groups was also statistically significant.

Neoplastic findings in the kidney, liver, and pituitary are amongst the most common tumors found in control CD-1 mice (Baldrick P & Reece L, 2007). Other findings (adenocarcinoma of epididymides & rhabdomyosarcoma of seminal vesicles) were sporadic and considered to be rare (Sanghvi DA et al. 2004).

Toxicokinetics

Blood samples were taken at 4 and 24 hours post-dose in weeks 4 and 26; and at 1, 4, 12 and 24 hours post-dose in week 52

Summary of Week 52 toxicokinetics

Dose (mg/kg)	Sex	t_{max} (h)	C_{max} (ng/mL)	C_{max}/Dose (kg·ng/mL/mg)	$AUC_{(0-24)}$ (ng·h/mL)	$AUC_{(0-24)}$/Dose (h·kg·ng/mL/mg)
20	M	4	71.6	3.58	353	17.6
	F	1	67.7	3.39	353	17.7
150	M	4	625	4.17	3080	20.5
	F	4	823	5.49	3690	24.6
500	M	4	910	1.82	5190	10.4
	F	4	1670	3.34	7870	15.7

Summary: Fulvestrant exposure (C_{max} and $AUC_{(0-24)}$) increased in a dose proportional manner between 20 and 150 mg/kg and less than dose proportional between 150 and 500 mg/kg. There were no gender differences in exposure.

Dosing Solution Analysis

The analytical procedure was validated with respect to linearity of detector response, precision of injection, specificity of chromatographic analysis, limit of detection, accuracy and precision. The mean concentrations of fulvestrant in test formulations analyzed for the study were within ±10% of nominal concentrations, confirming accurate formulation.

All mice dosed with fulvestrant were proven to be exposed to fulvestrant, except for a few mice given the low dose (20 mg/kg); however, they were only sampled at 24 hours when the levels would be expected to be under LLOQ.

11 Integrated Summary and Safety Evaluation

The carcinogenic potential of fulvestrant was evaluated in a 104-week CD-1 mouse study. The design of the study was acceptable and based on previous toxicology studies and/or the guidance of the ECAC. An increase in benign and malignant granulosa cell tumors, benign luteomas, benign sex cord stromal tumors, and tubulostromal adenomas in the ovary was observed with fulvestrant treatment. It was determined that these findings could be combined into benign and malignant sex cord stromal tumors for labeling purposes based on the origin of each tumor type. Consistent with the pharmacology of fulvestrant, increases in atrophy of the female reproductive tract were observed. These findings are consistent with the carcinogenicity findings in female rats with fulvestrant administration, which included increases in ovarian granulosa cell tumors. Although increases in interstitial Leydig cell tumors were seen in the rat study, no correlative findings were seen in male mice.

The clinical AUC was measured over a period of 30 days as the clinical administration schedule is once per month and the half life ($t_{1/2}$) of fulvestrant in patients is approximately 40 days. The half life of fulvestrant in mice after daily oral administration ranged from 4-8 hours, and the AUC was measured over a period of 24 hours (i.e., $AUC_{0\text{-}24h}$). Therefore, to obtain a comparable AUC between mice in this carcinogenicity study and humans administered a monthly dose of 500 mg fulvestrant via intramuscular injection, the $AUC_{0\text{-}24h}$ values in mice were multiplied by 30 days, resulting in an $AUC_{0\text{-}30\ days}$ value. The following table provides the animal to human exposure ratios ($AUC_{0\text{-}30\ days}$) based on a 30 day AUC.

Species	Dose	C_{max} (ng/mL)	$AUC_{0\text{-}30\ days}$ (ng*h/mL)	Animal:human exposure ratio
				$AUC_{0\text{-}30\ days}$
Human (Day 90)	500 mg once monthly	280	13100	-
Males				
Mouse (Day 52)	20 mg/kg/day	71.6	10590	0.80
	150 mg/kg/day	625	92400	7.05
	500 mg/kg/day	910	155700	11.89
Females				
Mouse (Day 52)	20 mg/kg/day	67.7	10590	0.80
	150 mg/kg/day	823	110700	8.45
	500 mg/kg/day	1670	236100	18.02

Carcinogenicity conclusion:

Positive; under the conditions tested, fulvestrant was carcinogenic.

12 Appendices/Attachments

Appendix A

Executive CAC
February 12, 2008

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
John Leighton, Ph.D., DDOP, Alternate Member
Bill Taylor, Ph.D., DSPTP, Alternate Member
Leigh Verbois, Ph.D., DDOP, Supervisor
Todd Bourcier, Ph.D., DMEP, Team Leader
Gemma Kuijpers, Ph.D., DMEP, Presenting Reviewer

Author of Draft: Gemma Kuijpers

The following information reflects a brief summary of the Committee discussion and its recommendations. The committee did not address the sponsor's proposed statistical evaluation for the 2-yr carcinogen bioassay, as this does not affect the sponsor's ability to initiate the bioassay. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2006).

IND#: 62,195
Drug Name: Fulvestrant
Sponsor: AstraZeneca

Background
Fulvestrant is an anti-estrogen that blocks the action of estrogen without significant partial estrogen agonist activitry. Faslodex™ was approved in 2002 for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. The recommended dose is 250 mg/month (4 mg/kg/month). A two-year intramuscular carcinogenicity study was conducted in rats and was reviewed by ECAC as part of NDA 21-344. In rats, at doses up to 5x (females) and 2x (males) human exposure there was an increased incidence of benign ovarian granulosa cell tumors and testicular Leydig cell tumors.

(b) (4) (b) (4) precocious puberty associated with McCune
Albright Syndrome (MAS) in pediatric girls (b) (4)
Doses to be used are 4 mg/kg/month in pediatric girls with MAS, (b) (4)

(b) (4)

(b) (4)

(b) (4)

On October 25, 2005, ECAC discussed the design of an oral mouse carcinogenicity study with doses of 20, (b) (4) 500 mg/kg/day and a coconut oil vehicle/cremophor formulation. The vehicle was used to increase systemic exposure. The Committee concurred with the 500 mg/kg high dose selection based on 25-fold multiplicity of anticipated monthly exposure (AUC) in the mouse vs. AUC in women at the approved 250 mg/month dose. The Committee also concurred with the 20 mg/kg low dose but recommended a mid dose of 150 mg/kg. (b) (4)

(b) (4)

Mouse Carcinogenicity Study Protocol and Dose Selection

Sponsor proposes a 2-year oral gavage carcinogenicity study in CD1 mice with **0 (water), 0 (vehicle control), 0 (vehicle control), 20, 150, 500 mg/kg/day**. Both vehicle control groups are dosed with coconut oil formulation (Imwitor 988, Cremophor RH40, Miglycol 812N, ethanol) diluted 1:2 in water. Dose groups receive stock solutions diluted 1:2 in water to yield doses of 20, 150, 500 mg/kg. Dose volume is 10 mL/kg. Sponsor stated that (b) (4)

(b) (4)

(b) (4) The Sponsor is asking for ECAC concurrence with a high dose of 500 mg/kg based on MFD. The Sponsor also asks for concurrence with the 2-year mouse study to complete the carcinogenicity evaluation for Faslodex.

A 3-month oral gavage toxicity study was conducted in CD mice. Dose groups included water, coconut oil vehicle (1:5 or 1:2 dilution in water), 100, 200, 500 mg/kg/day (1:5, 1:5, 1:2 water dilutions). Data showed toxicity of the coconut vehicle evidenced by decreased food intake and body weight gain in males (10%↓ at 1:2) and females (28%↓ at 1:5 and 13%↓ at 1:2). Fulvestrant induced an initial increase in body weight gain in both males and females, followed by a decrease in body weight gain in males and a continuing increase in females. Fulvestrant had effects in reproductive organs probably due to anti-estrogenic activity. Effects on kidney (prominent Bowman capsule in females, enlargement and cortical tubular hypertrophy in males), submandibular gland (granular duct hypertrophy), lymph node (multinucleate foamy macrophages) and lacrimal gland (swelling, hypertrophy) were of unclear origin.

Executive CAC Recommendations and Conclusions

- The Committee noted that the vehicle was needed to maximize exposure and that the vehicle was associated with toxicity in the 3-month study as reflected by reductions in body weight gain in females at both 1:5 and 1:2 dilutions and in males at 1:2 dilution.

- The Committee concurred that the 3-month study indicated that doses of 0 (water control), 0 (vehicle control), 0 (vehicle control), 20, 150, 500 mg/kg are acceptable for a 2-year study based on an expected 25-fold ratio of AUC exposure.
- However, the Committee noted that the vehicle toxicity may interfere with the interpretability of the study.
- The Committee commented that a study in male mice is more likely to be valid than a study in female mice, since males appear to be less sensitive to vehicle toxicity, but this was not assured.

Abigail Jacobs, Ph.D.
Acting Chair, Executive CAC

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

/s/

KIMBERLY R RINGGOLD
10/19/2012

TODD R PALMBY
10/22/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s020

STATISTICAL REVIEW(S)

SLR-019

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

CARCINOGENICITY STUDY

IND/NDA Number:	IND 52,121/NDA 21-344
Drug Name:	Fulvestrant
Indication(s):	104 Week Carcinogenicity Study in Mice
Applicant:	Sponsor: AstraZeneca Alderley Park, England SK104TG (b) (4)
Documents Reviewed:	Electronic submission: Received date March 30, 2011 Electronic data submission: Dated May 15, 2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -6
Statistical Reviewer:	Mohammad Atiar Rahman, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Hematology Oncology Toxicology Products
Reviewing Pharmacologist:	Kimberly Ringgold, Ph.D.
Project Manager:	Kim Robertson
Keywords:	Carcinogenicity, Dose response relationship

Table of Contents

Background

In this submission the sponsor included a report of an animal carcinogenicity study in mice. This study was intended to assess the carcinogenic potential of Fulvestrant in mice when administered once daily via gavage at appropriate drug levels for 104 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. Ringgold.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

Design

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one water control group, and two vehicle control groups. The dose levels for treated groups were 20, 150, and 500 mg/kg/day. In this review these dose groups were referred to as the low, medium, and high dose groups, respectively. The animals in the water control group received vehicle (water for injection), and the vehicle control groups received placebo (Placebo for ICI 182,780 oral solution) by gavage. Initially, three hundred and forty two Crl:CD1(ICR) mice of each sex were planned to be randomly divide into the six treatment groups with equal size of fifty seven animals. The sponsor's report states that an additional cohort of five females were assigned to the water control group and to the high dose group to run six weeks after the main study animals, following a high number of deaths due to mis-dosing accidents in Week 1 in the high dose group. These mice were also treated for 104 weeks. However, the submitted data showed that there were 60, 57, 57, 60, 61, and 58 male mice, and 63, 57, 57, 61, 60, and 65 female mice in the water control, vehicle 1, vehicle 2, low, medium, and high dose groups, respectively.

During the study all animals were inspected at least twice daily for the evidences of ill-health or reaction to treatment. A detailed physical examination was carried out once each week. Once each week, in conjunction with the detailed physical examination, palpation was performed upon each animal. Particular attention was paid to any superficial or palpable swellings, for which the location, size, consistency, time of first observation and subsequent history were recorded. A complete necropsy was performed in all animals died naturally, killed moribund, or terminally sacrificed at the end of the study.

The body weight of each mouse was recorded one week before treatment commenced (Week -1), on the day that treatment commenced (Week 0), twice weekly for Week 1 to 4, weekly for Weeks 5 to 16, once every 2 weeks for Weeks 17 to 28, once every 4 weeks thereafter, and before necropsy.

1.1. Sponsor's analyses

1.1.1. Survival analysis

The sponsor presented the numbers of animals died and their estimated proportion during the study as life tables and Kaplan-Meier survival curves (Kaplan and Meier 1958) and analyzed the data using the log rank tests for a trend across the groups (Mantel 1966, Peto 1974). The following statistical tests were carried out:

1) A two-tailed test for a trend with dose level for low, medium, and high dose groups with the pooled vehicle control groups.

2) A two-tailed pairwise comparison test of each treatment group and the water control group against the pooled vehicle control groups.

Where the test for trend was statistically significant, the highest dose group was excluded and the trend test was repeated, until the test was no longer statistically significant

In their analysis the sponsor considered the death of animals # 497, 505, 552, 834, 853, 854, 857, 871 and 872 as accidental death and treated them as censored during their analysis.

Sponsor's findings: Sponsor's analysis showed 21 (37%), 24 (42%), 31 (54%), 19 (33%), 18 (32%), and 21 (37%) survival of male mice, and 27 (44%), 21 (37%), 23 (40%), 23 (40%), 24 (42%), and 27 (44%) survival of female mice in water control, vehicle control 1, vehicle control 2, low, medium and high dose groups, respectively.

The sponsor's analysis did not show statistically significant positive dose response relationship in either sex when the data from pooled vehicle control, low, medium, and high dose were included in the analysis. Also none of the pairwise comparisons were statistically significant in either sex.

1.1.2. Tumor data analysis

The sponsor analyzed the tumor data for dose response relationship and pairwise comparisons of treated groups and controls, using the data from pooled vehicle control, low, medium, and high dose groups. The trend tests were performed using the mortality adjusted method outlined by Peto et al. (1980), and the pairwise comparisons were performed using the Fisher exact test.

The following tumors pools were defined for dose response relationship analysis in addition to individual tumor analysis:

1. Lung: Alveolar Bronchiolar Adenoma and Alveolar Bronchiolar Carcinoma
2. Liver: Hepatocellular Adenoma and Hepatocellular Carcinoma
3. Skin/Subcutis: Fibrosarcoma, Malignant Fibrous Histiocytoma and malignant Schwannoma
4. Duodenum: Adenocarcinoma and Adenoma; Jejunum: Adenocarcinoma; Colon: Adenoma
5. Ovaries: Granulosa Cell Tumor Benign, Granulosa Cell Tumor Malignant; Luteoma Benign, Sex Cord Stromal Tumor Benign, Sex Cord Stromal Tumor Malignant, Tubulostromal Adenoma and Cystadenoma.
6. Uterus: Adenomatous Polyp, Stromal Polyp and Adenocarcinoma
7. Testis: Leydig Cell Tumor Benign and Leydig Cell Tumor Malignant
8. Haemangiosarcoma from the following primary sites: Lung, Liver, Ovaries, Uterus, Spleen, Mesenteric Lymph Node, Skin/Subcutis, Skeletal Muscle and Femerotibial joint.

Adjustment for multiple testing: In the submitted study report the sponsor did not mention of any adjustment procedure for multiple testing.

Sponsor's findings:

Comparison of Water control and Vehicle control groups:

The sponsor's analysis showed no statistically significant difference in the incidence of any of the observed tumors in either sex . The sponsor stated that the range of neoplastic lesions seen in the water control group and the vehicle control groups were similar and were of the types expected in this strain of mouse.

Comparison of Pooled vehicle control groups and treatment groups:

The sponsor summarized their findings as follows:

Female treated animals showed a treatment related increase in the incidences of various ovarian tumors (Sex cord stromal tumor benign, sex cord stromal tumor malignant, granulosa cell tumor benign, granulosa cell tumor malignant, luteoma benign, and tubulostromal adenoma). The test for each of these tumors separately and when pooled showed statistically significant dose response reationship for increased incidences. On pairwise testing the increased incidence reached statistical significance from 150 mg/kg/day.

The pair-wise comparisons also showed a small number of tumors to have statistically significant differences in their incidences between treated and pooled vehicle control groups. The sponsor considered these findings to be unrelated to treatment with Fulvestrant due to them occurring in isolated groups/sex and lack of statistical significance on Peto trend testing.

1.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

As stated in Section 2 of this review, the experiment had one water control and two vehicle control groups. To analyze data from experiments having both untreated and vehicle control groups, the FDA statististical guidance for carcinogenicity data analysis suggests using the data from the vehicle control group(s) along with the data from the treated groups for appropriate interpretation of the carcinogenic drug effect of the study compounds. The FDA guidance also suggests to pool the identical control groups for relevant data analysis. Such pooling of identical controls increases the power of the tests. Following these suggestions given in the FDA guidance, this reviewer conducted the primary analysis of mortality and tumor data using the data from the pooled vehicle control along with the data from the treated groups. Some secondary analyses were also performed for additional exploration of the data including data from the water control group.

1.2.1. Survival analysis

The survival distributions of animals in all six treatment groups were estimated by the Kaplan-Meier product limit method separately for males and females. The dose response relationship of mortality was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female mice, respectively. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed 21 (35%), 24 (42%), 31 (54%), 19 (32%), 18 (30%), and 21 (36%) overall survival of male mice in water control, vehicle control 1, vehicle control 2, low, medium, and high dose groups, respectively and 27 (45%), 21 (37%), 23 (40%), 23 (38%), 24 (39%), and 27 (47%) overall survival of female mice in water control, vehicle control 1, vehicle control 2, low, medium, and high dose groups, respectively. This reviewer's analysis did not show statistically significant dose response relationship in mortality across pooled vehicle control group, low medium and high dose groups in either sex. The pairwise comparisons also did no show statistically significant increased mortality in any of the treated groups compared to the water control or the pooled vehicle control group in either sex. There was not statistically significant difference in mortality between the water control and the pooled vehicle control.

Reviewer's comment: *The number of survivors in different groups calculated by the sponsor and this reviewer matches in both sexes. However the there were some differences in the percentages of survivors calculated by the sponsor and this reviewer in few treatment groups. These differences were due to the fact that in their percentage calculation the sponsor used 57for all treatment groups in males, and 62, 57, 57, 57, 57, and 62 as the denominator for water control, vehicle control 1, vehicle control 2, low, medium, and high dose groups, respectively in females. These numbers are the initially planned group size plus 5 animals added to the female water control group and high dose group due to misdosing deaths. On the other hand, this reviewer used the number of animals in each treatment group included in the submitted data, namely 60, 57, 57, 60, 61, and 58 in male mice, and 63, 57, 57, 61, 60, and 65 in female mice as the denominator for water control, vehicle control 1, vehicle control 2, low, medium, and high dose groups, respectively.*

1.2.2. Tumor data analysis

This reviewer analyzed the tumor data for dose response relationships among the pooled vehicle control, low, medium, and high dose groups, and pairwise comparisons of pooled vehicle control group with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of s_h =1. An animal that dies at week w_h without a tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k$ <1. The adjusted group size is defined as $N^* = \Sigma s_h$. As an interpretation, an animal with score s_h =1 can be considered as a whole animal while an animal with score s_h <1 can be considered as a partial animal. The adjusted group size N^* is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male and female mice, respectively.

Multiple testing adjustment: For the adjustment of multiple testing of dose response relationship, the FDA guidance for the carcinogenicity study design and data analysis suggests the use of test levels of α=0.005 for common tumors and α=0.025 for rare tumors for a submission with two species, and a significance level of α=0.01 for common tumors and α=0.05 for rare tumors for a submission with one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one for which the published spontaneous tumor rate is less than 1%. For multiple pairwise comparisons of treated group with

control the FDA guidance suggests the use of test levels α=0.01 for common tumors and α=0.05 for rare tumors, in order to keep the false-positive rate at the nominal level of approximately 10% for both submissions with two or one species.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Reviewer's findings: Following tumor types showed p-values less than or equal to 0.05 either for dose response relationship or pairwise comparisons of treated groups with vehicle control.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons in Mice Using the Vehicle Control

			Vehicle	20 mg	150 mg	500 mg	P-Value			
Sex	Organ Name	Tumor Name	Cont	Low	Med	High	Dose Resp	VC vs L	VC vs M	VC vs H
Male	SKIN/SUBCUTIS	Malignant Fibrous Histiocytoma	0	5	1	0	0.8494	0.0028*	0.3333	.
Female	ADRENAL GLANDS	Subcapsular Cell Adenoma	1	2	4	1	0.4673	0.2245	0.0357*	0.5538
	LUNG	Alveolar/bronchiolar carcinoma	3	1	2	5	0.0259	0.7837	0.5027	0.0782
	OVARIES	Benign granulosa cell tumor	2	3	13	10	<0.001*	0.1742	<0.001*	<0.001*
		Benign luteoma	0	2	16	11	<0.001*	0.0968	<0.001*	<0.001*
		Hemangioma	0	3	1	0	0.7007	0.0277*	0.3140	.
		Malignant granulosa cell tumor	0	2	12	9	<0.001*	0.0933	<0.001*	<0.001*
		Sex Cord Stromal Tumor Benign	3	2	7	12	<0.001*	0.4909	0.0119	<0.001*
		Tubulostromal adenoma	0	0	6	4	0.0085*	.	<0.001*	0.0108*

Based on the criteria of adjustment for multiple testing discussed above, the dose response relationship for the incidences of ovarian benign granulosa cell tumor, benign luteoma, malignant granulosa cell tumor, benign sex cord stromal tumor, and tubulostromal adenoma in female mice were considered to be statistically significant. The pairwise comparison p-values marked by the asterisks were also considered to be statistically significant for the increased incidences of the associated tumor type and treated group compared to the pooled vehicle control.

Reviewer's comment: *The sponsor's analysis showed significant increased incidence of malignant sex cord stromal tumor, but this reviewer's analysis did not show statistically significant dose response relationship for incidence of this tumor type. This reviewer's analysis showed an incidence rate of 0, 0, 0, and 1 tumor bearing animals in the pooled control, low, medium, and high dose groups, respectively, with the dose response relationship p-value of 0.2020. The sponsor's analysis also showed the same incidence rates i.e. 0, 0, 0, and 1 tumor bearing animals in the pooled control, low, medium, and high dose groups, respectively. Their p-values for the dose response relationship test or pairwise comparisons were not reported.*

Analysis using the untreated control group: In order to verify the sponsor's findings this reviewer performed some additional analyses using the data from the water control. The results are shown in Tables 4A and 4B in the appendix for mate and female mice. The results of comparison of water and vehicle controls are shown in Tables 5A and 5B in the appendix for mate and female mice. The following table shows this reviewer's significant findings:

Significant Dose Response Relationship or Pairwise Comparisons

in Mice Using the Water Control

Sex	Organ Name	Tumor Name	Water Cont	20 mg Low	150 mg Med	500 mg High	P-Value Dose Resp	P-Value WC vs L	P-Value WC vs M	P-Value WC vs H
Female	LIVER	Hepatocellular adenoma	0	0	3	3	0.0436*	.	0.1071	0.1160
	OVARIES	Benign granulosa cell tumor	1	3	13	10	0.0082*	0.2707	<0.001*	0.0036*
		Benign luteoma	2	2	16	11	0.0073*	0.6534	<0.001*	0.0076*
		Malignant granulosa cell tumor	0	2	12	9	0.0048*	0.2162	<0.001*	0.0012*
		Sex Cord Stromal Tumor Benign	0	2	7	12	<0.001*	0.2162	0.0044*	<0.001*
		Tubulostromal adenoma	0	0	6	4	0.0322*	.	0.0092*	0.0551

Comparison of Water and Pooled Vehicle control groups

Male No statistically significant difference in any of the observed tumor type

Female No statistically significant difference in any of the observed tumor type

The results showed statistically significant findings in all tumor types as were found using the pooled vehicle control group. In addition liver hepatocellular adenoma also showed statistically significant positive dose response relationship. No statistically significant difference was found in the incidence of any of the observed tumor types between the water control group and the pooled vehicle control group.

1.3. Summary

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one water control group, and two vehicle control groups. The dose levels for treated groups were 20, 150, and 500 mg/kg/day. The animals in the water control group received vehicle (water for injection), and the vehicle control groups received placebo (Placebo for ICI 182,780 oral solution) by gavage. Initially, three hundred and forty two Crl:CD1(ICR) mice of each sex were planned to be randomly divide into the six treatment groups with equal size of fifty seven animals. The sponsor's report states that an additional cohort of five females were assigned to the water control group and to the high dose group to run six weeks after the main study animals, following a high number of deaths due to mis-dosing accidents in Week 1 in the high dose group. These mice were also treated for 104 weeks. The submitted data, however, showed that 60, 57, 57, 60, 61, and 58 male mice, and 63, 57, 57, 61, 60, and 65 female mice were treated in the water control, vehicle 1, vehicle 2, low, medium, and high dose groups, respectively.

During the study all animals were inspected at least twice daily for the evidences of ill-health or reaction to treatment. A detailed physical examination was carried out once each week. Once each week, in conjunction with the detailed physical examination, palpation was performed upon each animal. Particular attention was paid to any superficial or palpable swellings, for which the location, size, consistency, time of first observation and subsequent history were recorded. A complete necropsy was performed in all animals died naturally, killed moribund, or terminally sacrificed at the end of the study.

The body weight of each mouse was recorded one week before treatment commenced (Week -1), on the day that treatment commenced (Week 0), twice weekly for Week 1 to 4, weekly for Weeks 5 to 16, once every 2 weeks for Weeks 17 to 28, once every 4 weeks thereafter, and before necropsy.

Results: The tests did not show statistically significant dose response relationship in mortality across pooled vehicle control group, low medium and high dose groups in either sex. The pairwise comparisons also did no

show statistically significant increased mortality in any of the treated groups compared to the untreated control group or the pooled vehicle control group in either sex. There was not statistically significant difference in mortality between the water control group and the pooled vehicle control group.

The tests showed statistically significant positive dose response relationship in the incidences of ovarian benign granulosa cell tumor, benign luteoma, malignant granulosa cell tumor, benign sex cord stromal tumor, and tubulostromal adenoma in female mice. The following pairwise comparisons were also considered to be statistically significant for the increased incidences of the associated tumor type and treated group compared to the pooled vehicle control.

Significant Pairwise Comparisons in Mice

Sex	Organ Name	Tumor Name	Dose Groups Compared with Pooled Vehicle Control
Male	SKIN/SUBCUTIS	Malignant Fibrous Histiocytoma	Low dose group
Female	ADRENAL GLANDS	Subcapsular Cell Adenoma	Medium dose group
	OVARIES	Benign granulosa cell tumor	Medium and high dose groups
		Benign luteoma	Medium and high dose groups
		Hemangioma	Low dose group
		Malignant granulosa cell tumor	Medium and high dose groups
		Sex Cord Stromal Tumor Benign	High dose groups
		Tubulostromal adenoma	Medium and high dose groups

Mohammad Atiar Rahman, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D.
Team Leader, Biometrics-6

cc:
Archival IND 52,121/NDA 21-344

Dr. Ringgold
Ms. Robertson

Dr. Machado
Dr. Lin
Dr. Rahman
MS. Patrician

Appendix

Table 1A: Intercurrent Mortality Rate
Male Mice

	Water Control		Veh. Control 1		Veh. Control 2		20 mg|kg|day		150 mg|kg|day		500 mg|kg|day	
	No. of		No. of		No. of		No. of		No. of		No. of	
Week	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %
0 - 52	9	15.00	8	14.04	7	12.28	10	16.67	7	11.48	13	22.41
53 - 78	16	41.67	10	31.58	12	33.33	12	36.67	13	32.79	13	44.83
79 - 91	4	48.33	8	45.61	5	42.11	9	51.67	16	59.02	5	53.45
92 - 104	10	65.00	7	57.89	2	45.61	10	68.33	7	70.49	6	63.79
Ter. Sac.	21	35.00	24	42.11	31	54.39	19	31.67	18	29.51	21	36.21
Total	N=60		N=57		N=57		N=60		N=61		N=58	

Table 1B: Intercurrent Mortality Rate
Female Mice

	Water Control		Veh. Control 1		Veh. Control 2		20 mg|kg|day		150 mg|kg|day		500 mg|kg|day	
	No. of		No. of		No. of		No. of		No. of		No. of	
Week	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %	Death	Cum. %
0 - 52	10	16.67	5	8.77	4	7.02	8	13.33	6	9.84	14	24.14
53 - 78	11	35.00	7	21.05	8	21.05	15	38.33	15	34.43	8	37.93
79 - 91	4	41.67	7	33.33	10	38.60	8	51.67	10	50.82	8	51.72
92 - 104	11	60.00	17	63.16	12	59.65	7	63.33	5	59.02	8	65.52
Ter. Sac.	27	45.00	21	36.84	23	40.35	23	38.33	24	39.34	27	46.55
Total	N=63		N=57		N=57		N=61		N=60		N=65	

Table 2A: Intercurrent Mortality Comparison
Male Mice

		P-Value Using	
Test	Statistic	Water Control	Vehicle Control
Dose-Response	Likelihood Ratio	0.9317	0.2604
Homogeneity	Log-Rank	0.9856	0.1417

Table 2B: Intercurrent Mortality Comparison
Female Mice

		P-Value Using	
Test	Statistic	Water Control	Vehicle Control
Dose-Response	Likelihood Ratio	0.9415	0.8065
Homogeneity	Log-Rank	0.9292	0.8182

Figure 1A: Kaplan-Meier Survival Functions for Male Mice

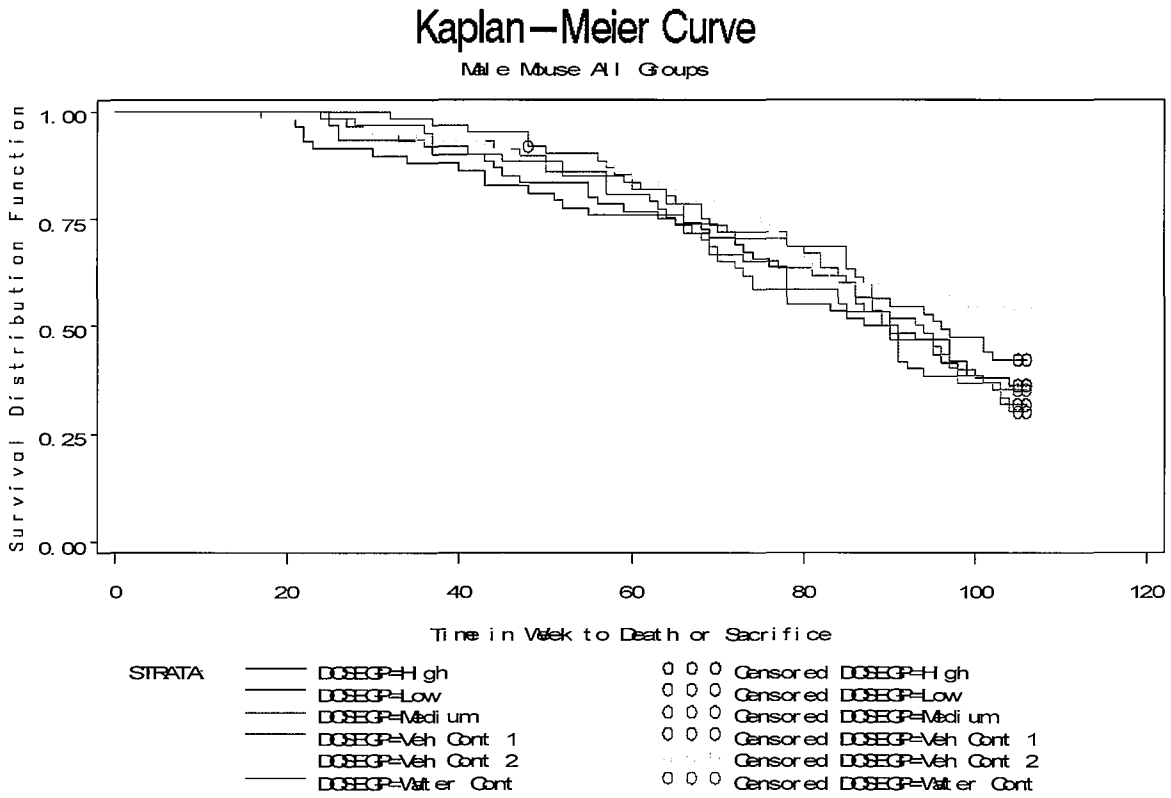
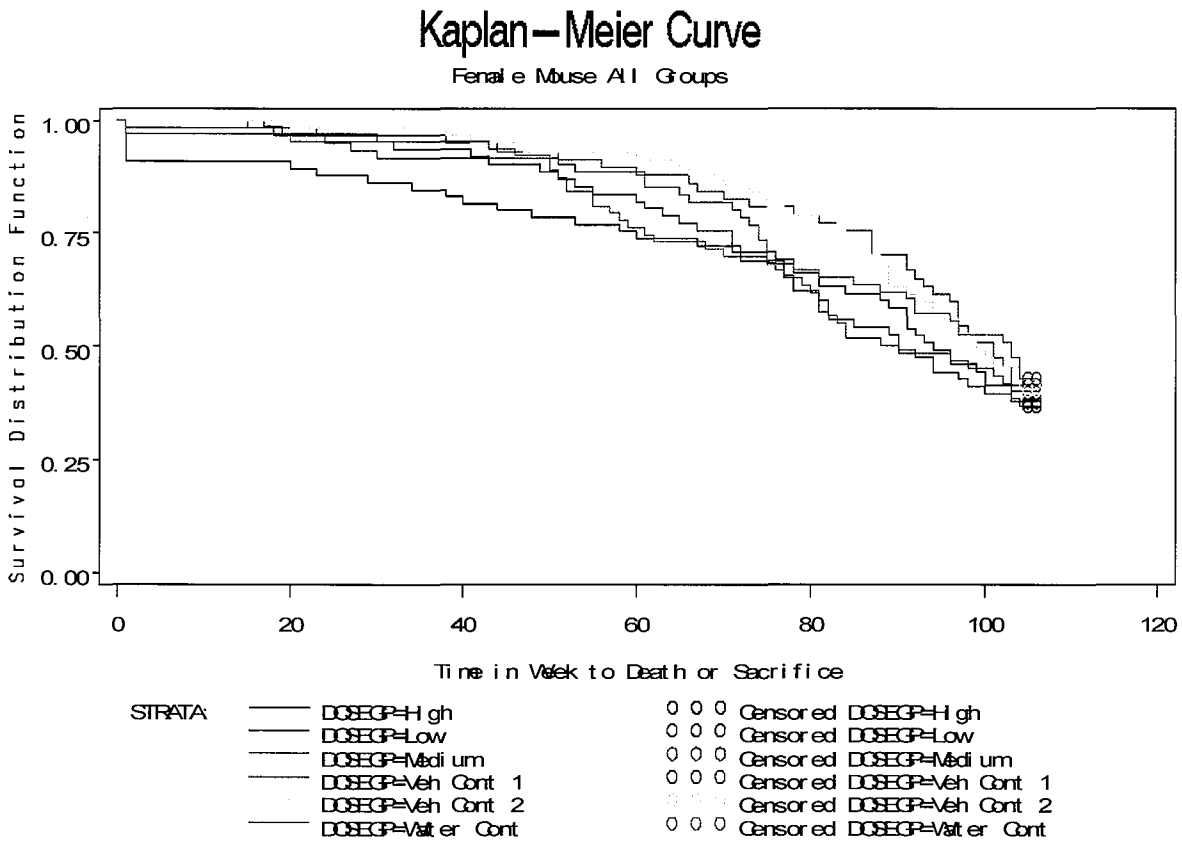


Figure 1B: Kaplan-Meier Survival Functions for Female Mice



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/s/

MOHAMMAD A RAHMAN
10/02/2012

KARL K LIN
10/24/2012
Concur with review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s020

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

REV-CLINPHARM-02 (Review Noted (NAI))
NDA-021344
SUPPL-20
Supporting Document 686
New/Supplement
Form 3674
Submit Date: 06/28/2012 - FDA Received Date: 06/28/2012

No clinical issues are to be addressed in thie labeling supplement.

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/s/

SAFAA BURNS
07/20/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s020

OTHER REVIEW(S)

Division of OHOP/DDOP1

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: IND 021344/ S-019 and S-020

Name of Drug: Faslodex® (fulvestrant) 500 mg, Injection

Applicant: AstraZeneca Pharmaceuticals LP

Labeling Review

Submission Date: June 28, 2012

Receipt Date: June 28, 2012

Background and Summary Description: This s-020 supplement provides an update to the overall survival results from "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 (D6997C00002), also known as the 'Confirm' study".

Review

NDA 021344 is approved for treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

This prior approval supplement (S-020) provides for the following edits to the package insert: Section 14 – Clinical Trials to add OS analysis.

This CBE supplement (S-019) provides for the following edits to the package insert: Section 6.2 and 13.1 updated post-marketing safety data from a mouse carcinogenicity, mutagenesis and impairment of a fertility study.

NDA 021344 s-019 and s-020 were bundled together for this review.

S-019 was reviewed by the non-clinical reviewer (see review dated 10/19/2012) and consultant to the CDER Carcinogenicity assessment committee (CAC) (see review dated 9/27/2012

S-020 was reviewed by the clinical and statistical reviewers (see review date: statistical XX/XX/2012 and clinical XX/XX/XXXX) and discussed in an internal labelling meeting.

Recommendations

FDA and sponsor have agreed to the labeling for s-019 and s-020

Regulatory Project Manager Date

Chief, Project Management Staff Date

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

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/s/

TECHIYA TOAFF
11/05/2012

ALICE KACUBA
11/05/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 19, 2012

To: Techiya Toaff, Regulatory Project Manager
Division of Oncology Products 1 (DOP1)

From: Gina McKnight-Smith, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)

CC: Karen Rulli, Professional Review Team II Leader, DPDP
Marybeth Toscano, Regulatory Review Officer, DPDP
Michelle Safarik, Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)

Subject: Comments on draft labeling (Package Insert) for Faslodex® (fulvestrant) Injection
NDA 021344, S-019 and S-020

In response to your consult request dated August 29, 2012, we have reviewed the draft Package Insert (PI) for Faslodex that includes the changes for S-019 and S-020. DPDP used the version of the PI titled, "FDA revisions_Oct 11 2012_S-019 and S-020_annotated-draft-label-28jun2012.doc" sent via email to OPDP by Techiya Toaff on October 17, 2012.

We have no comments at this time.

Thank you for the opportunity to consult on the proposed labeling.

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/s/

GINA P MCKNIGHT-SMITH
10/19/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 021344	NDA Supplement #:S- 020	Efficacy Supplement Type SE- 8
Proprietary Name: Faslodex® Established/Proper Name: (fulvestrant) Injection Dosage Form: Injection Strengths: 250 mg/5 mL		
Applicant: AstraZeneca Pharmaceuticals Agent for Applicant (if applicable): N/A		
Date of Application: June 28, 2012 Date of Receipt: June 28, 2012 Date clock started after UN:		
PDUFA Goal Date: December 28, 2012	Action Goal Date (if different): December 7, 2012	
Filing Date: Aug 27, 2012	Date of Filing Meeting: Aug 27, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) N/A		
Proposed indication(s)/Proposed change(s): This supplemental application proposes the following change(s): to provide the results of overall survival data from a Randomized, 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 (D6997C00002), also known as the 'CONFIRM' study.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***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***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic	

	☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ 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) ☐ 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): IND 062195	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, 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 no, 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			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, 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/OMPQ 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 Unacceptable for Filing (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

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 is 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)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***			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.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **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 314.108(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 (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***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.***			X	

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			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

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.	X			
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			X	
Applications in "the Program" (PDUFA V) (NME NDAs/Original BLAs)	**YES**	**NO**	**NA**	**Comment**
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			X	
• If yes, were all of them submitted on time?			X	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			X	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			X	
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 per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?			X	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?		x		
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**

Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***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? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	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 [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	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	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**

For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:			X	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***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 by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***			x	
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)***[3]				
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***			X	
REMS	**YES**	**NO**	**NA**	**Comment**

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		X		
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 applicant to submit SPL before the filing date.***	x			
Is the PI submitted in PLR format?[4]	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 applicant to submit labeling in PLR format before the filing date.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?			x	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?			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?				

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

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?				
Other 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:***		X		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***			X	
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***			X	
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***			X	

ATTACHMENT

MEMO OF FILING MEETING

DATE: 8/27/2012

NDA/Supp #: 050778 s-019

PROPRIETARY NAME: Faslodex®

ESTABLISHED/PROPER NAME: (fulvestrant) Injection

DOSAGE FORM/STRENGTH: 250 mg/5 mL

APPLICANT: AstraZeneca Pharmaceuticals

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): This supplemental application proposes the following change(s): to provide the results of overall survival data from a Randomized, 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

BACKGROUND:
This supplement was submitted to provide the results of overall survival data from a Randomized, 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 (D6997C00002), also known as the 'CONFIRM' study.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Techiya Toaff	Y
	CPMS/TL:	Kacuba Alice	Y
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Tatiana Prowell	Y
	TL:	Amy Mckee	Y
Social Scientist Review (*for OTC*	Reviewer:	N/A	

products)			
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:		
Clinical Pharmacology	Reviewer:	Safaa Burns	N
	TL:	Qi Liu	N
Biostatistics	Reviewer:	Somesh Chattopadhyay	Y
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Kimberly Ringgold	Y
	TL:	Todd Palmby	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Yong De Lu	N
	TL:	Haripada Sarker	N
Quality Microbiology *(for sterile products)*	Reviewer:	N/A	
	TL:		
CMC Labeling Review	Reviewer:	N/A	
	TL:		
Facility Review/Inspection	Reviewer:	N/A	
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	N/A	
	TL:		

OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	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**:	☐ 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?	☐ YES

Comments: ***If no, for an NME NDA or original BLA , 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***	Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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
Environmental Assessment • 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
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	 ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Division – Amna Ibrahim, M.D.

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): N/A per team

21st Century Review Milestones (see attached) (listing review milestones in this document is 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 any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	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 OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in "the Program")
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

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

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

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

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

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

/s/

TECHIYA TOAFF
09/05/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Techiya Toaff OHOP/DOP1

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
August 29, 2012	N/A	021344 s-020	Efficacy supplement

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Faslodex (fulvestrant) Injection		Oncology	TBD when SCPI is ready

NAME OF FIRM:	
AstraZeneca	PDUFA Date: Friday, December 28, 2012

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:

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.
We will send SCPI when ready and will provide a due date for your review then.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: Not needed per team
Labeling Meetings: TBD
Wrap-Up Meeting: TBD

6 Month priority review
PDUFA goal date: December 28, 2012, however target date for action is December 7, 2012.

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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

/s/

TECHIYA TOAFF
08/29/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021344Orig1s020

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 021344 SUPPL # -020 HFD # 150

Trade Name Faslodex®

Generic Name N/A

Applicant Name AstraZenaca

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(1), SE8

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?

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# 21344

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:

"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."

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"):

"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."

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 # 52121 and 62195		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: Techiya Toaff
Title: RPM
Date: October 22, 2012

Name of Office/Division Director signing form: Amna Ibrahim, M.D.
Title: Deputy Division Director

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

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

/s/

TECHIYA TOAFF
11/09/2012

AMNA IBRAHIM
11/09/2012

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 # S-019 and S-020 BLA Supplement #	If NDA, Efficacy Supplement Type: SE8 (S-20) SLR (0-19)
Proprietary Name: Faslodex® Established/Proper Name: fulvestran Dosage Form: 250 mg/5 mL Injection		Applicant: AstraZeneca Agent for Applicant (if applicable):
RPM: Techiya Toaff		Division: DOP1

NDAs and NDA Efficacy Supplements:

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.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] 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 12/28/12	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[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.

[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

NDA # 021344
SLR-019
S-020

❖ 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
❖ Application Characteristics [3]	

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

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

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 ASCO 11/1/12

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.

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S - 020

‣ 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

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SCR-019
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- [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).*

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(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[4]	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) Draft
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.	S-020: October 19, 2012
• Original applicant-proposed labeling	S-019: May 15, 2012 S-020: June 28, 2012
• Example of class labeling, if applicable	N/A

[4] Fill in blanks with dates of reviews, letters, etc.

NDA # 0213
SCR-019
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Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	N/A
• Original applicant-proposed labeling	N/A
• 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	N/A
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	N/A
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM S-019 11/08/12 S-020 09/05/12 ☐ DMEPA ☐ DMPP/PLT (DRISK) ☒ ODPD (DDMAC) 10/19/12 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	RPM 9/5/12
❖ 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 _____ If PeRC review not necessary, explain: SE8 • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

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❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	x
❖ Internal memoranda, telecons, etc.	N/A
❖ 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
• 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)	N/A
• 48-hour alert or minutes, if available *(do not include transcript)*	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	TL co-signed clincial review dated 11/02/12
• Clinical review(s) *(indicate date for each review)*	
• 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)*	See MOR
❖ 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

[6] Filing reviews should be filed with the discipline reviews.

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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 Co-signed clinical review dated 11/02/12
Statistical Review(s) *(indicate date for each review)*	☐ None C-signed clinical review dated 11/02/12
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
❖ 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 co-signed review 10/22/12
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 10/22/12
❖ 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 10/24/12
❖ ECAC/CAC report/memo of meeting	☐ None 9/27/12 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
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None

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❖ 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)*	
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ 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[7])*	Date completed: ☐ 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)

[7] 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.

Toaff, Techiya

From: Toaff, Techiya
Sent: Tuesday, October 16, 2012 4:49 PM
To: Troise, Nicholas J
Cc: Kacuba, Alice; Robertson, Kim
Subject: NDA 021344 s-019 and s-020 __ Faslodex

Importance: High

Attachments: Agreed _S-019 received October 10, 2012 annotated-draft-label-2012oct.doc; FDA revisions_Oct 11 2012_S-019 and S-020_annotated-draft-label-28jun2012.doc

Dear Nicholas,

We attempt to bundle NDA 021344 s-019 and s-020, since all FDA comments in s-019 have been accepted by you.

Please find attached:
1. FDA revised label in track changes combining both labels (s-019 and s-020).
2. FDA revised label in track changes accepted by you on October 10, 2012.

Please submit an official label amendment to include both s-019 and s-020 by Friday, Oct 19, 2012, along with an email courtesy copy to me.
When you reply we require a clean word version to the agreed upon revisions.

Thank you,
Thea


Agreed _S-019 received October...


FDA revisions_Oct 11 2012_S-01...

Thank you,

Thea

Techiya (Thea) Toaff , R.N., B.S.N.
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
US Food and Drug Administration
White Oak Bldg 22, Room 5103
10903 New Hampshire Avenue
Silver Spring, MD 20993
(office) 301-796-2103 | (fax) 301-796-9845 |
E-mail: techiya.toaff@fda.hhs.gov

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/s/

TECHIYA TOAFF
10/16/2012

S-019

Executive CAC
Date of Meeting: September 18, 2012

Committee: David Jacobson Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Sushanta Chakder, Ph.D., DGIEP, Alternate Member
Todd Palmby, Ph.D, DHOT, Acting Team Leader
Kimberly Ringgold, Ph.D, DHOT, Presenting Reviewer

Author of Draft: Kimberly Ringgold, Ph.D

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 21344
Drug Name: Faslodex® (fulvestrant)
Sponsor: AstraZeneca Pharmaceuticals

Background:

Faslodex® (fulvestrant) is an estrogen receptor antagonist currently marketed for use in women with hormone receptor positive metastatic breast cancer. Fulvestrant was negative in a standard battery of genotoxicity assays. The standard 2-year rat bioassay was reviewed by the ECAC under the original NDA approval (b) (4) (b) (4) (b) (4) The protocol was reviewed and approved by the ECAC in 2008.

Mouse Carcinogenicity Study

Fulvestrant was administered to CD-1 mice (57/sex/group) at dose of 0 (water & vehicle controls), 20, 150, and 500 mg/kg fulvestrant given once daily for at least 104 weeks. The vehicle was Imwitor 988 43.11% w/w, Cremophor RH40 29.56% w/w, Miglyol 812-N 14.00% w/w, Ethanol 13.33% w/w. Additional animals in the toxicokinetic groups were administered the water control or the drug. Terminal sacrifice was at week 104 for all animals. Survival was adequate for analysis and there was no difference in survival amongst drug-treated mice compared to controls. Non-neoplastic findings included increased body weight gain in males and females as well as increases in macrophage aggregates in the mesenteric lymph nodes and atrophy of the female reproductive tract. Neoplastic findings included statistically significant increases in benign and malignant granulosa cell tumors, benign luteomas, benign sex cord stromal tumors, and tubulostromal adenomas in the ovary. These findings were considered to be drug related.

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee concurred that the study was acceptable despite the exposure in high-dose mice not quite being 25-fold the maximum human exposure, which was the primary basis for exec-CAC concurrence with the high-dose selection.

- The Committee concurred that the benign and malignant granulosa cell tumors, benign luteomas, benign sex cord stromal tumors, and tubulostromal adenomas in the ovaries of female mice were drug-related.

David Jacobson Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DOP1
/TPalmby, DHOT
/KRinggold, DHOT
/KRobertson, DOP1
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
09/27/2012

DAVID JACOBSON KRAM
09/27/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021344/S-020

FILING COMMUNICATION

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

Dear Mr. Troise:

Please refer to your Supplemental New Drug Application (sNDA) dated June 28, 2012, received, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Faslodex® (fulvestrant) Injection, 250 mg/5 mL.

We also refer to your amendment dated July 25, 2012.

This supplemental application proposes the following change(s): to provide the results of overall survival data from a Randomized, 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 (D6997C00002), also known as the 'CONFIRM' study.

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Priority**. Therefore, the user fee goal date is Friday, December 28, 2012.

We are reviewing your supplemental 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

proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 28, 2012.

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 supplemental application and is not indicative of deficiencies that may be identified during our review.

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.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call me, Regulatory Project Manager, at (301) 796 2103.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ALICE KACUBA
09/05/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Techiya Toaff OHOP/DOP1

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
August 29, 2012	N/A	021344 s-020	Efficacy supplement

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Faslodex (fulvestrant) Injection		Oncology	TBD when SCPI is ready

NAME OF FIRM:	
AstraZeneca	PDUFA Date: Friday, December 28, 2012

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:

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.
We will send SCPI when ready and will provide a due date for your review then.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: Not needed per team
Labeling Meetings: TBD
Wrap-Up Meeting: TBD

6 Month priority review
PDUFA goal date: December 28, 2012, however target date for action is December 7, 2012.

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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/s/

TECHIYA TOAFF
08/29/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 021344/S-020

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

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

Dear Mr. Troise:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 021344

SUPPLEMENT NUMBER: -020

PRODUCT NAME: Faslodex® (fulvestrant) Injection, 250 mg/5 mL

DATE OF SUBMISSION: June 28, 2012

DATE OF RECEIPT: June 28, 2012

This supplemental application proposes the following change(s): to provide the results of overall survival data from a Randomized, 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 (D6997C00002), also known as the 'CONFIRM' study.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 27, 2012, in accordance with 21 CFR 314.101(a).

If the application is filed, the goals date is TBD by the filling date.

If you have not already done so, promptly 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. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

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 Oncology Products 1
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me, at (301) 796-2103.

Sincerely,

{See appended electronic signature page}

Techiya (Thea) Toaff, R.N., BSN
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation and Research
techiya.toaff@fda.hhs.gov

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/s/

TECHIYA TOAFF
07/26/2012