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 U.S. 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

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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 days 1, 15, 29 and once monthly thereafter *[see Clinical Studies (14)]*.

2.2 Dose Modification

Hepatic Impairment:

A dose of 250 mg is recommended for patients with moderate hepatic impairment (Child-Pugh class B) to be administered intramuscularly into the buttock slowly (1 - 2 minutes) as one 5 mL injection on days 1, 15, 29 and once monthly thereafter. FASLODEX has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C) *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*.

2.3 Administration Technique

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

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

Remove perforated patient record label from syringe.

Peel open the safety needle (SafetyGlide™) outer packaging. For complete SafetyGlide™ instructions refer below to the "Directions for Use of SafetyGlide™".

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).

Twist to lock the needle to the luer connector.

Remove needle sheath.

Remove excess gas from the syringe (a small gas bubble may remain).

Administer intramuscularly slowly in the buttock.

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

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

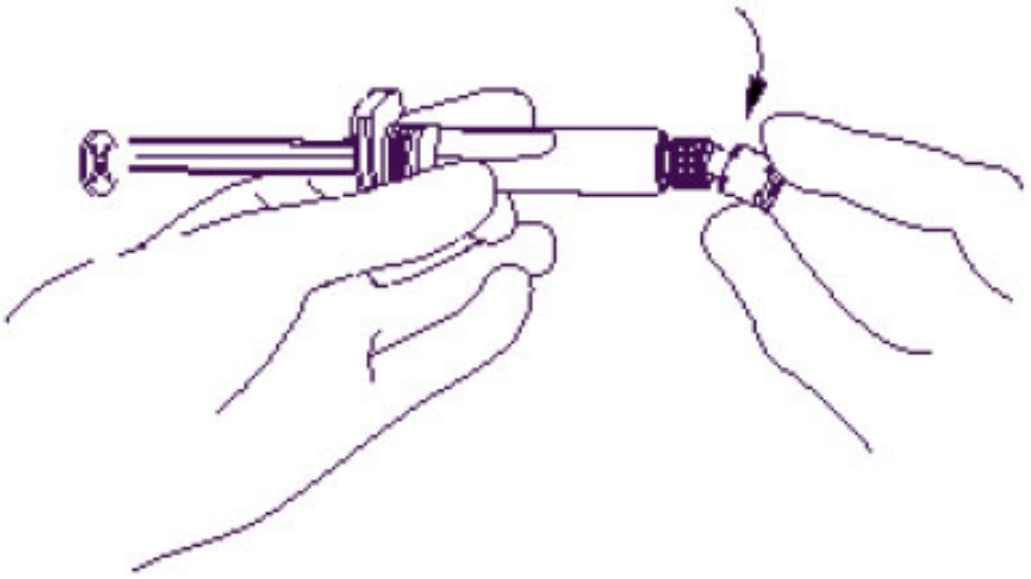


Figure 2

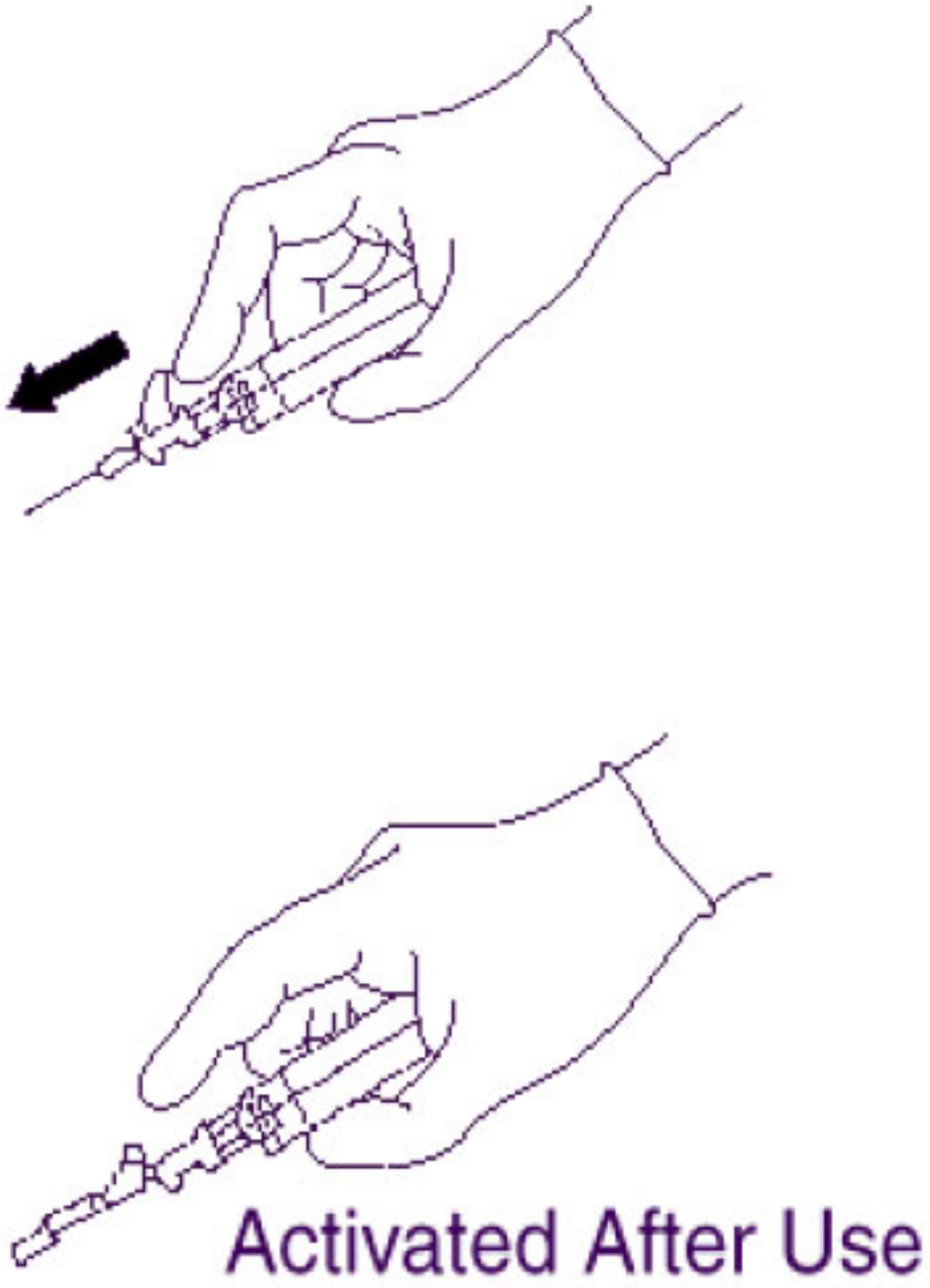
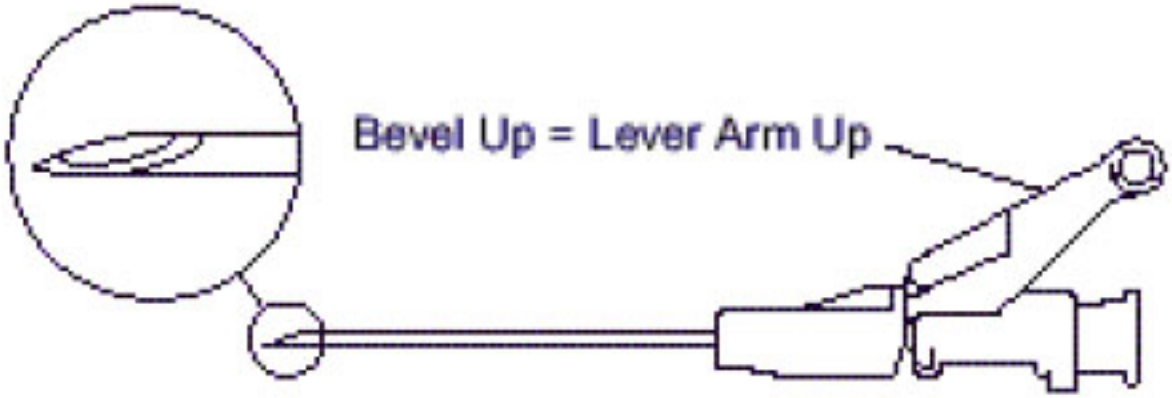


Figure 3



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*	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†	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 patient may have more than one adverse reaction.
†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 ($C_{min,}$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

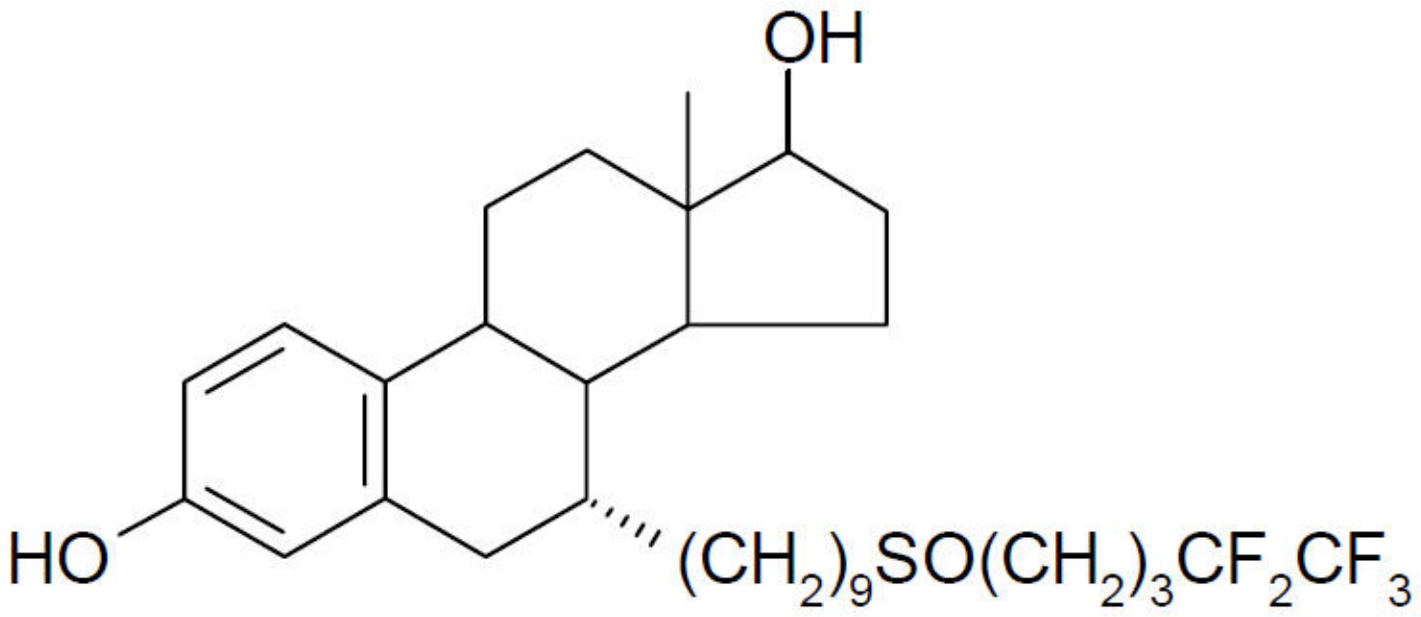
Negligible amounts of fulvestrant are eliminated in urine; therefore, a study in patients with renal impairment was not conducted. In the advanced breast cancer trials, fulvestrant concentrations in women with estimated creatinine clearance as low as 30 mL/min were similar to women with normal creatinine.

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
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. In addition, a two year carcinogenicity study was conducted in female and male mice at orally administered doses of 0, 20, 150 and 500 mg/kg/day. These doses correspond to 0, 0.8, 8.4 and 18 -fold (in females) and 0, 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 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[*] Median (months)	6.5	5.4
Hazard Ratio[†] (95% CI[‡])	0.80 (0.68-0.94)	
p-value	0.006	
OS[§] **Updated Analysis**[§] (% patients who died)	261 (72.1%)	293 (78.3%)
Median OS (months)	26.4	22.3
Hazard Ratio[†] (95% CI[‡])	0.81 (0.69-0.96)	
ORR[¶](95% CI[‡])	13.8% (9.7%, 18.8%) (33/240)	14.6% (10.5%, 19.4%) 38/261)

*PFS (Progression Free Survival) = the time between randomization and the earliest of progression or death from any cause. Minimum follow-u
duration of 18 months.
†Hazard ratio < 1 favors FASLODEX 500 mg.
‡CI=Confidence Interval
§OS=Overall Survival
¶ORR (Objective Response Rate), as defined as number (%) of patients with complete response or partial response, was analyzed in the evaluab
patients with measureable disease at baseline (fulvestrant 500 mg N=240; fulvestrant 250 mg N=261). Minimum follow-up duration of 18 mont

Figure 4 Kaplan-Meier PFS: Study 1 ITT Population

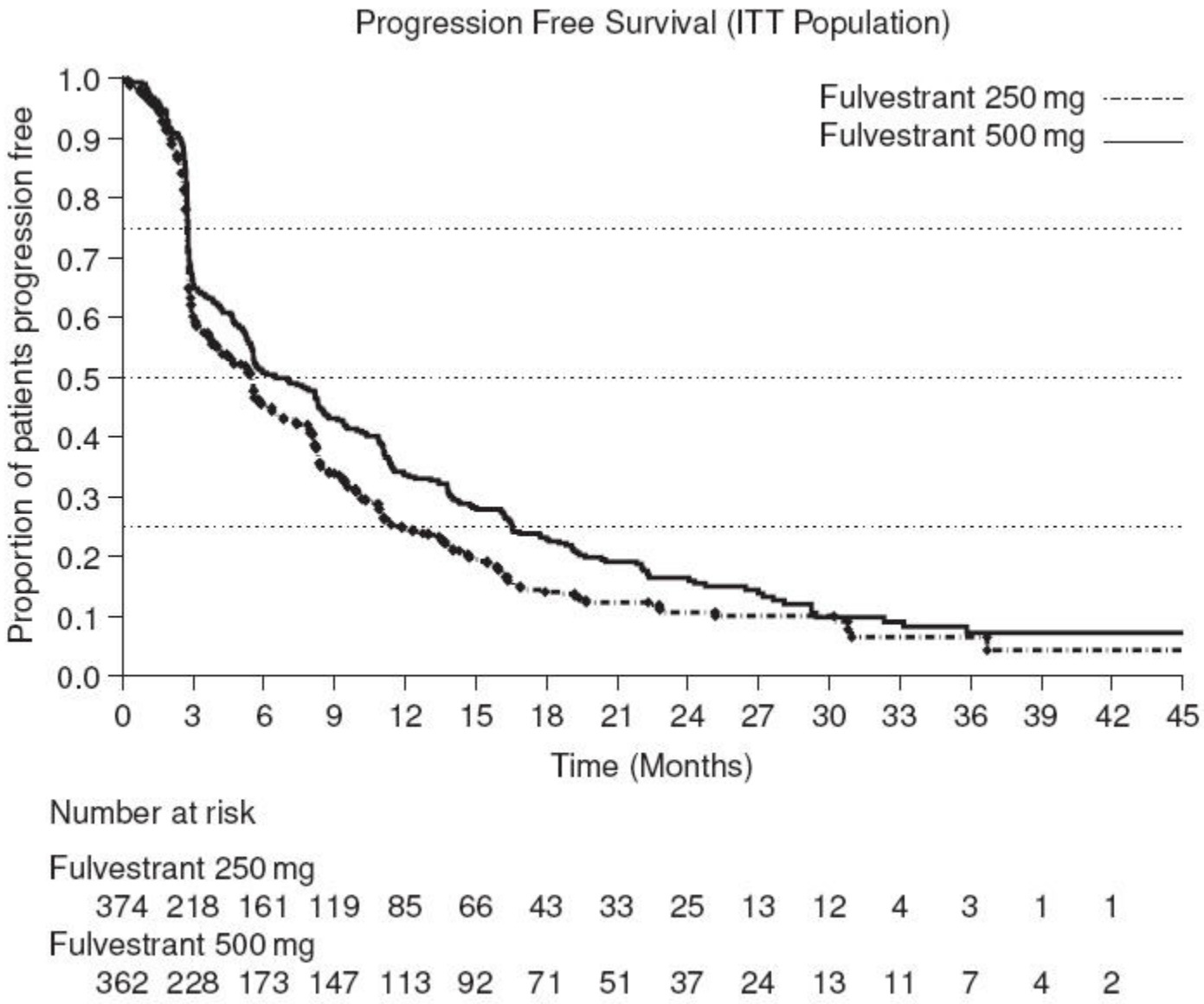
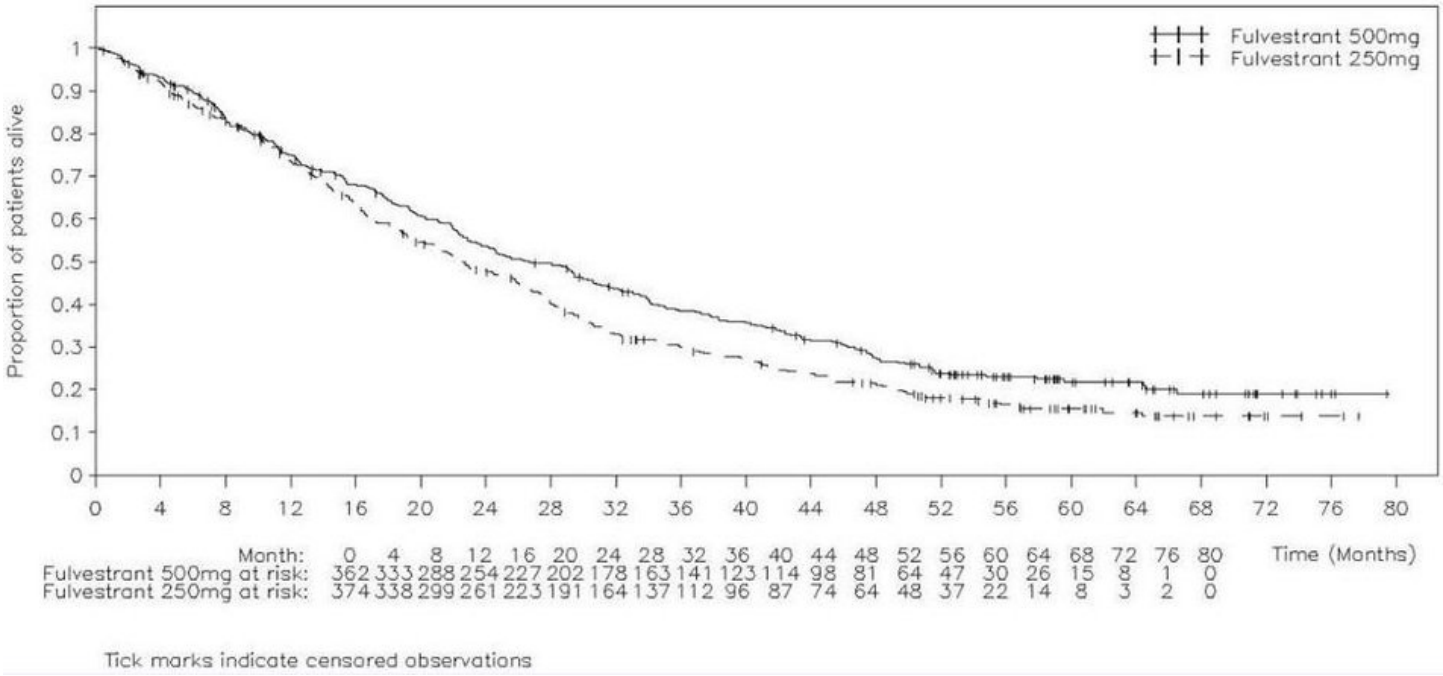


Figure 5 Kaplan-Meier OS (minimum follow-up duration of 50 months): Study 1 ITT Population



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 $\pm$ 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)**	
	FASLODEX	**Anastrozole**	**FASLODEX**	**Anastrozole**
Endpoint	**250 mg (n=206)**	**1 mg (n=194)**	**250 mg (n=222)**	**1 mg (n=229)**
Objective tumor response				
Number (%) of subjects with CR[*] + PR[†]	35 (17.0)	33 (17.0)	45 (20.3)	34 (14.9)
% Difference in Tumor Response Rate (FAS[‡] —ANA[§]) 2–sided 95.4% CI[¶]	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 [#] 2-sided 95.4% CI[¶]		0.9 (0.7, 1.1)		1.0 (0.8, 1.2)
Stable Disease for ≥ 24 weeks (%)	26.7	19.1	24.3	30.1
Overall Survival (OS)				
Died n (%) Median Survival (days)	152 (73.8%) 844	149 (76.8%) 913	167 (75.2%) 803	173 (75.5%) 736
Hazard Ratio[#] (2-sided 95% CI[¶])		0.98 (0.78, 1.24)		0.97 (0.78, 1.21)

*****CR = Complete Response
†PR = Partial Response
‡FAS = FASLODEX
§ANA = anastrozole
¶CI = Confidence Interval
#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.

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Ravensburg, Germany
Rev. 11/2012

PACKAGE/LABEL DISPLAY PANEL – 250 MG/5 ML (50 MG/ML)

NDC 0310-0720-10
For Single-Patient Use Only
FASLODEX®
Fulvestrant injection
250 mg/5 mL (50 mg/mL)
For Intramuscular Use Only

Revised: 11/2012

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