FASLODEX®
(fulvestrant)
injection

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: 09/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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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 antihormone therapy.

2 DOSAGE AND ADMINISTRATION

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

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

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

2.3 Administration Technique

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

1. Remove glass syringe barrel from tray and check that it is not damaged.
2. Remove perforated patient record label from syringe.
3. Peel open the safety needle (SafetyGlide™) outer packaging. For complete SafetyGlide™ instructions refer below to the "Directions for Use of SafetyGlide™.”
4. Break the seal of the white plastic cover on the syringe Luer connector and attach the SafetyGlide™ needle to the Luer Lock of the syringe by twisting.
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.

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.
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.

In the pooled safety population (N=1127) from clinical trials comparing FASLODEX 500 mg to FASLODEX 250 mg, post-baseline increases of ≥1 TCI 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)

Table 2 lists adverse reactions reported with an incidence of 5% or greater, regardless of whether considered causally, 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 1: Summary of Most Commonly Reported Adverse Reactions in Study 1 (≥5% in either treatment group): Safety Population

<table>
<thead>
<tr>
<th>Body System and Adverse Reaction</th>
<th>Fulvestrant 500 mg</th>
<th>Fulvestrant 250 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=361</td>
<td>N=374</td>
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<tr>
<td>Body as a Whole</td>
<td></td>
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<tr>
<td>Injection Site Pain</td>
<td>42 (11.6)</td>
<td>34 (9.1)</td>
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<tr>
<td>Headache</td>
<td>28 (7.8)</td>
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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 baseline 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, confusion, tachycardia, hot flush, extremity pain, and vomiting. Nine (30.0%) patients reported an AAE, 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 with EPP, compared with AAS. 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.

8.7 Renal Impairment

Fulvestrant 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 Warnings and Precautions (5.2)].

Fulvestrant and its major metabolites are not 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 overdose 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-pentafluoropentyloxy) nonyl]estr-1,3,5(10)-triene-3,17-beta-diol. The molecular formula is C32H47F5O3S and its structural formula is:

![Structural formula of fulvestrant](https://example.com/structure.png)

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 Benzate, USP, as co-solvents, and made up to 100% w/v with Castor Oil, USP as a co-solvent and release rate modifier.
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<sub>0-30 days</sub>] achieved in women receiving the recommended dose of 500 mg/mont. 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 antioestrogen.

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 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 (0.006% 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 anti-oestrogenic 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<sub>0-30 days</sub>] 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 33% of subjects had no measurable disease. Approximately 55% of patients had visceral disease.

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

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

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Fulvestrant 500 mg (N=362)</th>
<th>Fulvestrant 250 mg (N=374)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS* Median (months)</td>
<td>6.5</td>
<td>5.4</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.80 (0.68-0.94)</td>
<td>1.06</td>
</tr>
<tr>
<td>p-value</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>OS† Died</td>
<td>175 (48.3)</td>
<td>203 (54.3)</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>25.1</td>
<td>22.8</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.84 (0.99-1.03)</td>
<td>0.98</td>
</tr>
<tr>
<td>ORR* (95% CI)</td>
<td>13.8% (9.7%, 18.8%) (33/240)</td>
<td>14.6% (10.5%, 19.4%) (38/261)</td>
</tr>
</tbody>
</table>

* PFS (Progression Free Survival) – the time between randomization and the earliest of progression or death from any cause.
† Hazard ratio – CI: 95% Confidence Interval of Hazard Ratio.
‡ OS = Overall Survival
§ 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).

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 aromatase inhibitor or progesterin 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%; visceral – liver involvement 23.6%; lung involvement 28.1%; bone only 19.7%; soft tissue only 5.2%; skin and soft tissue 1.7%.

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

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Study 2</th>
<th>Study 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FASLODEX</td>
<td>Anastrozole</td>
</tr>
<tr>
<td></td>
<td>250 mg</td>
<td>1 mg</td>
</tr>
<tr>
<td></td>
<td>(n=206)</td>
<td>(n=194)</td>
</tr>
<tr>
<td>Objective tumor response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) of subjects with CR + PR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>35 (17.0)</td>
<td>33 (17.0)</td>
</tr>
<tr>
<td>% Difference in Tumor Response Rate (FAS&lt;sup&gt;c&lt;/sup&gt;-ANA&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>0.0 (-6.3, 8.9)</td>
<td>5.4 (-1.4, 14.8)</td>
</tr>
<tr>
<td>2-sided 95.4% CI&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to progression (TTP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median TTP (days)</td>
<td>165</td>
<td>103</td>
</tr>
<tr>
<td>Hazard ratio&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>2-sided 95.4% CI&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable Disease for ≥24 weeks (%)</td>
<td>26.7</td>
<td>19.1</td>
</tr>
<tr>
<td>Overall Survival (OS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died n (%)</td>
<td>152 (73.8%)</td>
<td>149 (76.8%)</td>
</tr>
<tr>
<td>Median Survival (days)</td>
<td>844</td>
<td>913</td>
</tr>
<tr>
<td>Hazard Ratio&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0.98</td>
<td>0.97</td>
</tr>
</tbody>
</table>

<sup>a</sup> CR = Complete Response  
<sup>b</sup> PR = Partial Response  
<sup>c</sup> FAS = FASLODEX  
<sup>d</sup> ANA = anastrozole  
<sup>e</sup> CI = Confidence Interval  
<sup>f</sup> 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)].
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.

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 breastfeed. 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 ingredients in FASLODEX?

Active ingredient: fulvestrant

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