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, for intramuscular use
Initial U.S. Approval: 2002

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

Indications and Usage (1)	03/2016
Dosage and Administration (2.1, 2.2, 2.3)	03/2016
Warnings and Precautions (5.3)	03/2016

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

FASLODEX is an estrogen receptor antagonist indicated for the:

- Treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. (1)
- Treatment of HR-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy. (1)

---------- 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 ----------

- Risk of Bleeding: Use with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use. (5.1)
- Increased Exposure in Patients with Hepatic Impairment: Use a 250 mg dose for patients with moderate hepatic impairment. (2.2, 5.2, 8.6)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.3, 8.1, 8.3)

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

- The most common 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. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 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 ----------

- Lactation: Advise not to breast-feed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Monotherapy

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

Combination Therapy with Palbociclib

FASLODEX is indicated for the treatment of HR-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

Monotherapy

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)].*

Combination Therapy with Palbociclib

When FASLODEX is used in combination with palbociclib, 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. The recommended dose of palbociclib is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Palbociclib should be taken with food. Please refer to the full prescribing information of palbociclib.

Pre/perimenopausal women treated with the combination FASLODEX plus palbociclib should be treated with luteinizing hormone-releasing hormone (LHRH) agonists according to current clinical practice standards *[see Clinical Studies (14)]*.

2.2 Dose Modification

Monotherapy

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)]*.

Combination Therapy with Palbociclib

When FASLODEX is used in combination with palbociclib, refer to monotherapy dose modification instructions for FASLODEX. Refer to the full prescribing information of palbociclib for its dose modification, management of toxicities, and for use with concomitant medication.

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 into the buttock slowly.
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.

Important Administration Information

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. Hands must remain behind the needle at all times during use and disposal.

Do not autoclave SafetyGlide™ Needle before use.

Parenteral drug products should be visually inspected for any particulate matter and discoloration prior to administration, whenever solution and container permit.

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

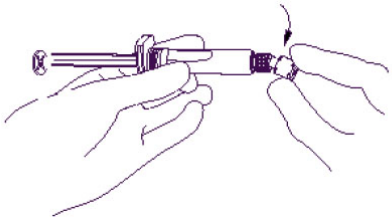


Figure 2

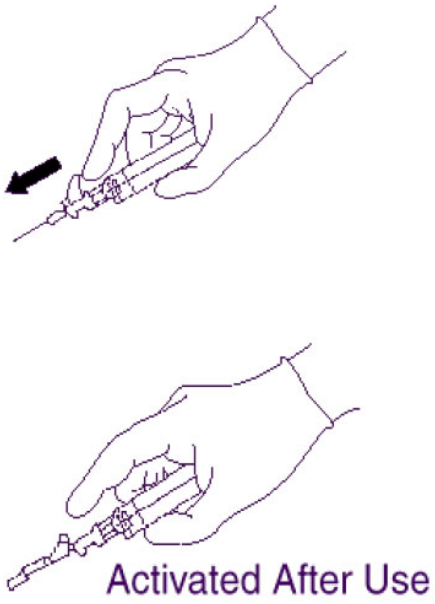
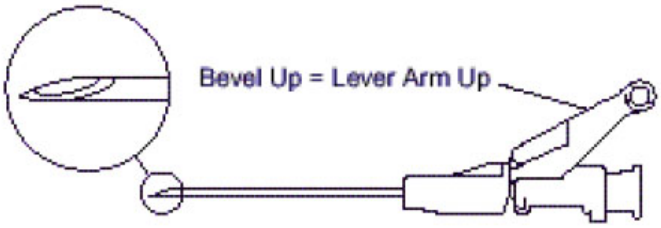


Figure 3



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 *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Bleeding

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

5.2 Increased Exposure in Patients with 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 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, FASLODEX can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of fulvestrant to pregnant rats and rabbits during organogenesis resulted in embryo-fetal toxicity at daily doses that are significantly less than the maximum recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with FASLODEX and for one year after the last dose *[see Use in Specific Populations (8.1), (8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Risk of Bleeding *[see Warnings and Precautions (5.1)]*
- Increased Exposure in Patients with Hepatic Impairment *[see Warnings and Precautions (5.2)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.3)]*

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.

Monotherapy

Comparison of FASLODEX 500 mg and FASLODEX 250 mg

The following adverse reactions (ARs) were calculated based on the safety analysis of Study 1 comparing the administration of FASLODEX 500 mg intramuscularly once a month with FASLODEX 250 mg intramuscularly once a month. 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 Study 1.

Table 1: Adverse Reactions in Study 1 (≥5% in Either Treatment Group)

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 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: Adverse Reactions in Studies 2 and 3 (≥5% from Combined Data)

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[1]	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

1. All patients on FASLODEX received injections, but only those anastrozole patients who were in the North American Study 2 received placebo injections.

Combination Therapy with Palbociclib

The safety of FASLODEX (500 mg) plus palbociclib (125 mg/day) versus FASLODEX plus placebo was evaluated in Study 4. The data described below reflect exposure to FASLODEX plus palbociclib in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of treatment in Study 4.

No dose reduction was allowed for FASLODEX in Study 4. Dose reductions of palbociclib due to an adverse reaction of any grade occurred in 36% of patients receiving FASLODEX plus palbociclib.

Permanent discontinuation associated with an adverse reaction occurred in 19 of 345 (6%) patients receiving FASLODEX plus palbociclib, and in 6 of 172 (3%) patients receiving FASLODEX plus placebo. Adverse reactions leading to discontinuation for those patients receiving FASLODEX plus palbociclib included fatigue (0.6%), infections (0.6%), and thrombocytopenia (0.6%).

The most common adverse reactions (≥10%) of any grade reported in patients in the FASLODEX plus palbociclib arm were neutropenia, leukopenia, infections, fatigue, nausea, anemia, stomatitis, headache, diarrhea, thrombocytopenia, constipation, vomiting, alopecia, rash, decreased appetite, and pyrexia.

The most frequently reported serious adverse reactions in patients receiving FASLODEX plus palbociclib were infections (3%), pyrexia (1%), neutropenia (1%), and pulmonary embolism (1%).

Adverse reactions reported in patients who received FASLODEX plus palbociclib in Study 4 are listed in Table 3, and laboratory abnormalities are listed in Table 4.

Table 3: Adverse Reactions in Study 4

Adverse Reaction	FASLODEX plus palbociclib (N=345)			FASLODEX plus placebo (N=172)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Infections and infestations						
Infections[a]	47	3	1	31	3	0
Blood and lymphatic system disorders						
Febrile neutropenia	1	1	0	1	0	1
Neutropenia	83	55	11	4	1	0
Leukopenia	53	30	1	5	1	1
Anemia	30	3	0	13	2	0
Thrombocytopenia	23	2	1	0	0	0
Eye disorders						
Vision blurred	6	0	0	2	0	0
Lacrimation increased	6	0	0	1	0	0
Dry eye	4	0	0	2	0	0
Metabolism and nutrition disorders						
Decreased appetite	16	1	0	8	1	0
Nervous system disorders						
Headache	26	1	0	20	0	0
Dysgeusia	7	0	0	3	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	7	0	0	2	0	0
Gastrointestinal disorders						
Nausea	34	0	0	28	1	0
Stomatitis[b]	28	1	0	13	0	0
Diarrhea	24	0	0	19	1	0
Constipation	20	0	0	16	0	0
Vomiting	19	1	0	15	1	0
Skin and subcutaneous tissue disorders						
Alopecia	18[c]	N/A	N/A	6[d]	N/A	N/A
Rash[e]	17	1	0	6	0	0
Dry skin	6	0	0	1	0	0
General disorders and administration site conditions						
Fatigue	41	2	0	29	1	0
Pyrexia	13	<1	0	5	0	0
Asthenia	8	0	0	5	1	0

Grading according to CTCAE 4.0.
CTCAE=Common Terminology Criteria for Adverse Events; N=number of patients; N/A=not applicable.

[a] Most common infections (>1%) include: nasopharyngitis, upper respiratory infection, urinary tract infection, influenza, bronchitis, rhinitis, conjunctivitis, pneumonia, sinusitis, cystitis, oral herpes, respiratory tract infection.

[b] Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, stomatitis.

[c] Grade 1 events – 17%; Grade 2 events – 1%.

[d] Grade 1 events – 6%.

[e] Rash includes: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, toxic skin eruption.

Table 4: Laboratory Abnormalities in Study 4

Laboratory Abnormality	FASLODEX plus palbociclib (N=345)			FASLODEX plus placebo (N=172)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	%	%	%	%	%	%
WBC decreased	99	45	1	26	0	1
Neutrophils decreased	96	56	11	14	0	1
Anemia	78	3	0	40	2	0
Platelets decreased	62	2	1	10	0	0

N=number of patients; WBC=white blood cells.

6.2 Postmarketing 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 CYP 3A4 inhibitors or inducers *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, FASLODEX can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of fulvestrant to pregnant rats and rabbits during organogenesis caused embryo-fetal toxicity, including skeletal malformations and fetal loss, at daily doses that were 6% and 30% of the maximum recommended human dose based on mg/m^2, respectively *[see Data]*. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Administration of fulvestrant to rats prior to and up to implantation caused embryonic loss at daily doses that were 0.6% of the daily maximum recommended human dose based on mg/m^2. When fulvestrant was administered to pregnant rats during the period of organogenesis, intramuscular doses ≥0.1 mg/kg/day (6% of the human recommended dose based on mg/m^2) caused 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 mg/m^2) and non-ossification of the odontoid and ventral tubercle of the first cervical vertebra at doses ≥0.1 mg/kg/day. Fulvestrant administered at 2 mg/kg/day caused fetal loss.

When administered to pregnant rabbits during the period of organogenesis, fulvestrant caused pregnancy loss at an intramuscular dose of 1 mg/kg/day (equivalent to the human dose based on mg/m^2). Further, at 0.25 mg/kg/day (30% the human dose based on mg/m^2), fulvestrant caused increases in placental weight and post-implantation loss in rabbits. 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 mg/m^2) when administered during the period of organogenesis.

8.2 Lactation

Risk Summary

There is no information regarding the presence of fulvestrant in human milk, nor of its effects on milk production or breast-fed infant. Fulvestrant can be detected in rat milk *[see Data]*. Because of the potential for serious adverse reactions in breast-fed infants from FASLODEX, advise a lactating woman not to breast-feed during treatment with FASLODEX and for one year after the final dose.

Data

Levels of fulvestrant were approximately 12-fold higher in milk than in plasma after exposure of lactating rats to a dose of 2 mg/kg. Drug exposure in rodent pups from fulvestrant-treated lactating dams was estimated as 10% of the administered dose. In a study in rats of fulvestrant at 10 mg/kg given twice or 15 mg/kg given once (less than the recommended human dose based on mg/m^2) during lactation, offspring survival was slightly reduced.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential within seven days prior to initiating FASLODEX.

Contraception

Females

FASLODEX can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment and for one year after the last dose.

Infertility

Based on animal studies, FASLODEX may impair fertility in females and males of reproductive potential. The effects of fulvestrant on fertility were reversible in female rats *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. 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, pruritus, 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 AUC_{ss} 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 Warnings and Precautions (5.2)]*.

8.7 Renal Impairment

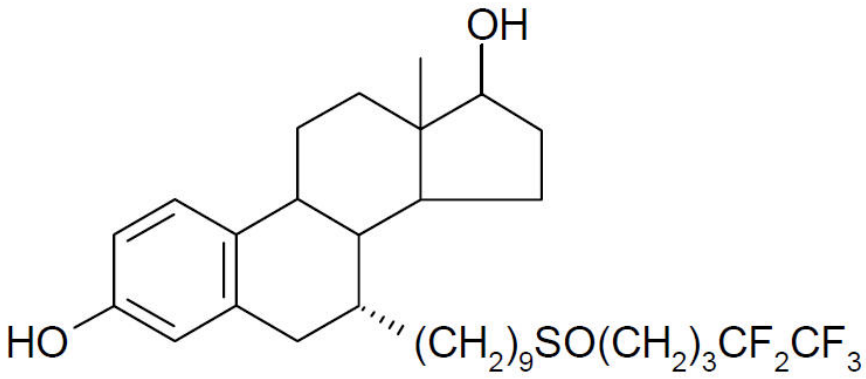
Negligible amounts of fulvestrant are eliminated in urine; therefore, a study in patients with renal impairment was not conducted. In the advanced breast cancer trials, fulvestrant concentrations in women with estimated creatinine clearance as low as 30 mL/min were similar to women with normal creatinine.

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 5. 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 5: 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[1]	Single dose	25.1 (35.3)	16.3 (25.9)	11400 (33.4)
	Multiple dose steady state[2]	28.0 (27.9)	12.2 (21.7)	13100 (23.4)

1. Additional 500 mg dose given on Day 15
2. 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 CYP 3A4, 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)]*. Data from a clinical trial in patients with breast cancer showed that there was no clinically relevant drug interaction between fulvestrant and palbociclib when the two drugs were co-administered.

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, 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 in mg/m^2]), 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 in mg/m^2). 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 in mg/m^2). 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. The efficacy of FASLODEX 500 mg in combination with palbociclib 125 mg was compared to FASLODEX 500 mg plus placebo in Study 4.

Monotherapy

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 6. 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 6: Efficacy Results Study 1: Intent-To-Treat (ITT) Population

Endpoint	**Fulvestrant 500 mg (N=362)**	**Fulvestrant 250 mg (N=374)**
PFS[1] Median (months)	6.5	5.4
Hazard Ratio[2] (95% CI[3])	0.80 (0.68-0.94)	
p-value	0.006	
OS[4] **Updated Analysis**[5] (% patients who died)	261 (72.1%)	293 (78.3%)
Median OS (months)	26.4	22.3
Hazard Ratio[2] (95% CI[3])[6]	0.81 (0.69-0.96)	
ORR[7] (95% CI[3])	13.8% (9.7%, 18.8%) (33/240)	14.6% (10.5%, 19.4%) 38/261)

1. 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.
2. Hazard Ratio <1 favors FASLODEX 500 mg.
3. CI=Confidence Interval
4. OS=Overall Survival
5. **Minimum follow up duration of 50 months.**
6. Not statistically significant as no adjustments were made for multiplicity.
7. ORR (Objective Response Rate), as defined as number (%) of patients with complete response or partial response, was analyzed in the evaluable patients with measureable 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

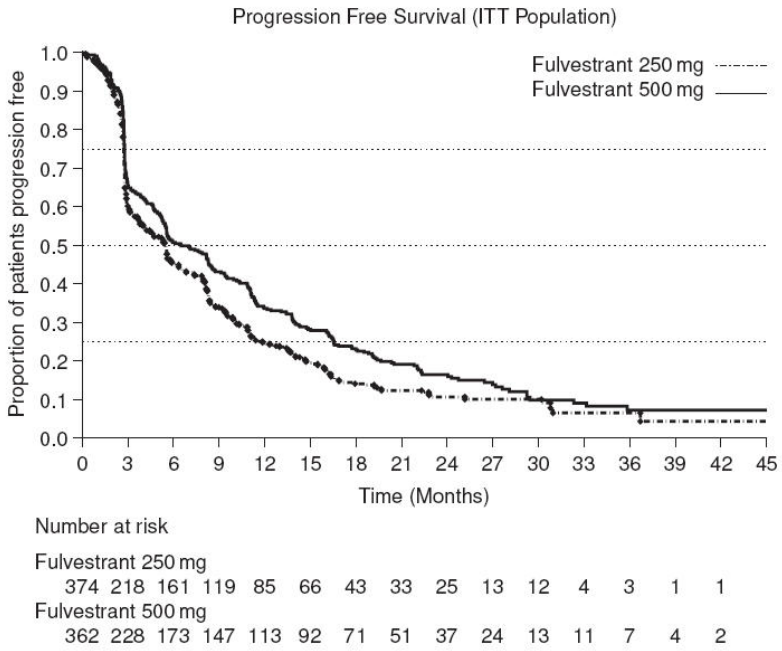
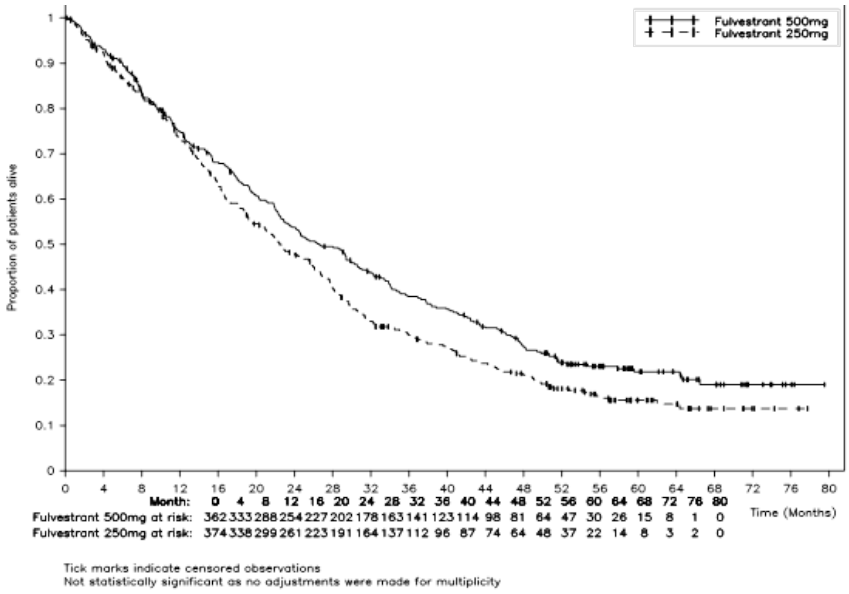


Figure 5 Kaplan-Meier OS (Minimum Follow-up Duration of 50 Months): Study 1 ITT Population



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 7. 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 7: 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[1] + PR[2]	35 (17.0)	33 (17.0)	45 (20.3)	34 (14.9)
% Difference in Tumor Response Rate (FAS[3]-ANA[4]) 2–sided 95.4% CI[5]	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 [6] 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 (%)	152 (73.8%)	149 (76.8%)	167 (75.2%)	173 (75.5%)
Median Survival (days)	844	913	803	736
Hazard Ratio[6]	0.98		0.97	

	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)**
(2-sided 95% CI)	(0.78, 1.24)		(0.78, 1.21)	

1. CR = Complete Response
2. PR = Partial Response
3. FAS = FASLODEX
4. ANA = anastrozole
5. CI = Confidence Interval
6. Hazard Ratio <1 favors FASLODEX

Combination Therapy

FASLODEX 500 mg in Combination with Palbociclib 125 mg (Study 4)

Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy

Study 4 was an international, randomized, double-blind, parallel group, multicenter study of FASLODEX plus palbociclib versus FASLODEX plus placebo conducted in women with HR-positive, HER2-negative advanced breast cancer, regardless of their menopausal status, whose diseased progressed on or after prior endocrine therapy.

A total of 521 pre/postmenopausal women were randomized 2:1 to FASLODEX plus palbociclib or FASLODEX plus placebo and stratified by documented sensitivity to prior hormonal therapy, menopausal status at study entry (pre/peri versus postmenopausal), and presence of visceral metastases. Palbociclib was given orally at a dose of 125 mg daily for 21 consecutive days followed by 7 days off treatment. Fulvestrant 500 mg was administered as two 5 mL injections each containing fulvestrant 250 mg/5mL, one in each buttock, on Days 1, 15, 29 and every 28 (+/- 3) days thereafter. Pre/perimenopausal women were enrolled in the study and received the LHRH agonist goserelin for at least 4 weeks prior to and for the duration of Study 4.

Patients continued to receive assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. The major efficacy outcome of the study was investigator-assessed PFS evaluated according to RECIST 1.1.

Patients enrolled in this study had a median age of 57 years (range 29 to 88). The majority of patients in each treatment arm were White (74%), all patients had an ECOG PS of 0 or 1, and 80% were postmenopausal. All patients had received prior systemic therapy and 75% of patients had received a previous chemotherapy regimen. Twenty-five percent of patients had received no prior therapy in the metastatic disease setting, 60% had visceral metastases, and 23% had bone only disease.

The results from the investigator-assessed PFS from Study 4 are summarized in Table 8 and Figure 6. Consistent results were observed across patient subgroups of disease site, sensitivity to prior hormonal therapy and menopausal status. Confirmed overall response rate in patients with measurable disease as

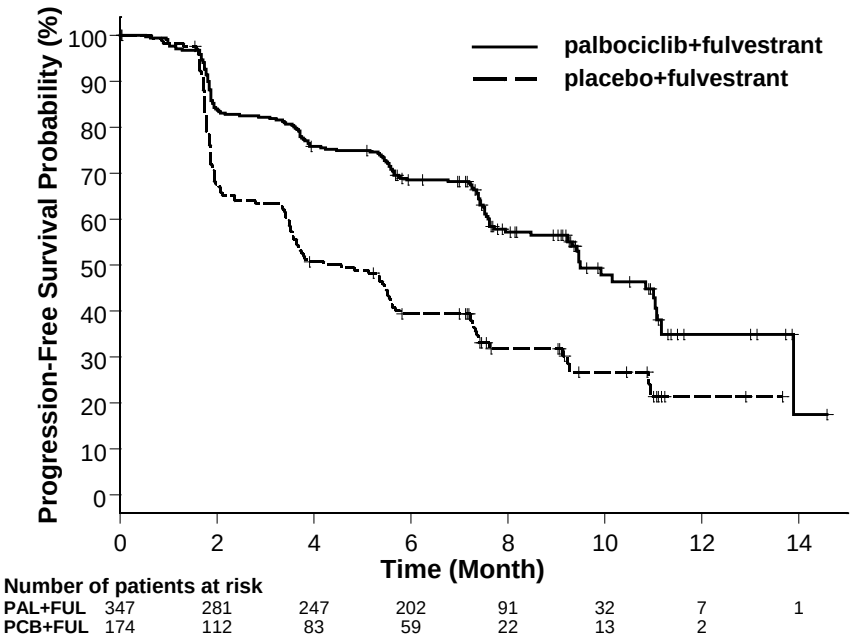
assessed by the investigator was 24.6% in the FASLODEX plus palbociclib and was 10.9% in the FASLODEX plus placebo arm. Duration of response was 9.3 months in the FASLODEX plus palbociclib arm compared with 7.6 months in the FASLODEX plus placebo arm. At the time of final analysis of PFS, OS data were not mature with 29% of events.

Table 8: Efficacy Results – Study 4 (Investigator Assessment, ITT Population)

	FASLODEX plus palbociclib (N=347)	**FASLODEX plus placebo (N=174)**
Progression-Free Survival		
Number of PFS Events (%)	145 (41.8%)	114 (65.5%)
Hazard Ratio (95% CI) and p-value	0.461 (0.360-0.591) p <0.0001	
Median PFS (months) (95% CI)	9.5 (9.2-11.0)	4.6 (3.5-5.6)

N=number of patients.
CI=confidence interval.

Figure 6 Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment, ITT Population) – Study 4



FUL=fulvestrant; PAL=palbociclib; PCB=placebo.

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

Advise the patient to read the FDA-approved patient labeling (Patient Information)

Monotherapy

Risk of Bleeding:

- 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)].*

Embryo-Fetal Toxicity:

- Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with FASLODEX and for one year after the last dose. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1), (8.3)].*

Lactation:

- Advise women not to breast-feed during treatment with FASLODEX and for one year after the last dose *[see Use in Specific Populations (8.2)]*.

Combination Therapy with Palbociclib

See palbociclib full prescribing information for Patient Counseling Information.

PATIENT INFORMATION

FASLODEX® (faz-lo-dex)

(fulvestrant)

Injection

What is FASLODEX?

FASLODEX is a prescription medicine used to treat:

- hormone receptor (HR)-positive breast cancer in women who have gone through menopause whose disease has spread after treatment with an antiestrogen medicine, OR
- HR-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer whose disease has spread to other parts of the body (metastatic) in combination with palbociclib in women with disease progression after hormonal therapy

When FASLODEX is used in combination with palbociclib, please also see the palbociclib Patient Information.

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

It is not known if FASLODEX is safe and effective in people with severe liver problems.

Who should not receive FASLODEX?

Do 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 receiving FASLODEX?

Before receiving FASLODEX, tell your healthcare provider about all of your medical conditions, including if you:

- have a low level of platelets in your blood or bleed easily.
- have liver problems.
- are pregnant or plan to become pregnant. FASLODEX can harm your unborn baby.
    - Females who are able to become pregnant should use effective birth control during treatment with FASLODEX and for one year after the last dose of FASLODEX.
    - Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with FASLODEX.
- are breast-feeding or plan to breast-feed. It is not known if FASLODEX passes into your breast milk. Do not breast-feed during your treatment with FASLODEX and for one year after the last dose of FASLODEX. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over the counter 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.

How will I receive FASLODEX?

- Your healthcare provider will give you FASLODEX by injection into the muscle of your buttock.
- Your healthcare provider may change your dose of FASLODEX if needed.

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
- shortness of breath
- constipation
- increased liver enzymes

FASLODEX may cause fertility problems in males and females. Talk to your healthcare provider if you plan to become pregnant.

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.

General information about the safe and effective use of FASLODEX

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use FASLODEX for a condition for which it was not prescribed. Do not give FASLODEX to other people, even if they have the same symptoms you have. It may harm them. 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.

What are the ingredients in FASLODEX?

Active ingredient: fulvestrant.

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

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

For more information, go to www.FASLODEX.com or call 1-800-236-9933.

This Patient Information has been approved by the U.S. Food and Drug Administration Revised: March 2016