

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

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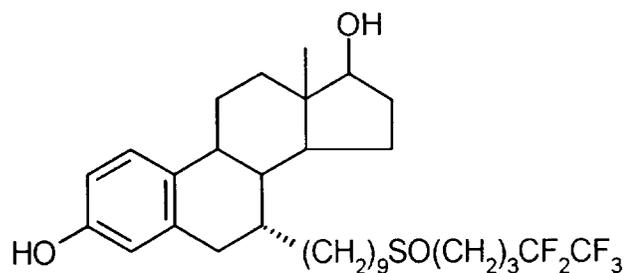


FASLODEX

(fulvestrant) Injection

DESCRIPTION

FASLODEX[®] (fulvestrant) Injection for intramuscular administration is an estrogen receptor antagonist without known agonist effects. The chemical name is 7- α -[9-(4,4,5,5,5-pentafluoropentylsulphonyl) nonyl]estra-1,3,5-(10)-triene-3,17- β -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: Alcohol, USP, Benzyl Alcohol, NF, and Benzyl Benzoate, USP, as co-solvents, and Castor Oil, USP as a co-solvent and release rate modifier.

FASLODEX is supplied in sterile single patient pre-filled syringes containing 50-mg/mL fulvestrant either as a single 5 mL or two concurrent 2.5 mL injections to deliver the required monthly dose. FASLODEX is administered as an intramuscular injection of 250 mg once monthly.

CLINICAL PHARMACOLOGY

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. Fulvestrant downregulates the ER protein in human breast cancer cells.

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.

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 resistant breast tumor xenografts may also be cross-resistant to tamoxifen.

Fulvestrant showed no agonist-type effects in *in vivo* uterotrophic 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.

Pharmacokinetics

Following intravenous administration, fulvestrant is rapidly cleared at a rate approximating hepatic blood flow (about 10.5 ml plasma/min/Kg). After an intramuscular injection plasma concentrations are maximal at about 7 days and are maintained over a period of at least one month, with trough concentration about one-third of C_{max}. The apparent half-life was about 40 days. After administration of 250 mg of fulvestrant intramuscularly every month, plasma levels approach steady-state after 3 to 6 doses, with an average 2.5 fold increase in plasma AUC compared to single dose AUC and trough levels about equal to the single dose C_{max} (see Table 1).

Table 1: Summary of fulvestrant pharmacokinetic parameters in postmenopausal advanced breast cancer patients after intramuscular administration of a 250 mg dose (Mean ± SD)

	C _{max} ng/ml	C _{min} ng/ml	AUC ng.d/ml	t _{1/2} days	CL ml/min
Single dose	8.5 ± 5.4	2.6 ± 1.1	131 ± 62	40 ± 11	690 ± 226
Multiple dose steady state	15.8 ± 2.4	7.4 ± 1.7	328 ± 48		

Fulvestrant was subject to extensive and rapid distribution. The apparent volume of distribution at steady state was approximately 3 to 5 L/kg. This suggests that distribution is largely extravascular. Fulvestrant was 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 and Excretion:

Biotransformation and disposition of fulvestrant in humans have been determined following

intramuscular and intravenous administration of ¹⁴C-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.

Fulvestrant was rapidly cleared by the hepatobiliary route with excretion primarily via the feces (approximately 90%). Renal elimination was negligible (less than 1%).

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 apparent 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.

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.

Hepatic Impairment-- Fulvestrant is metabolized primarily in the liver. In clinical trials in patients with locally advanced or metastatic breast cancer, pharmacokinetic data were obtained following administration of a 250 mg dose of FASLODEX to 261 patients classified as having normal liver function and to 24 patient with mild impairment. Mild impairment was defined as an alanine aminotransferase concentration (at any visit) greater than the upper limit of the normal (ULN) reference range, but less than 2 times the ULN; or if any 2 of the following 3 parameters were between 1- and 2-times the ULN: aspartate aminotransferase, alkaline phosphatase, or total bilirubin.

There was no clear relationship between fulvestrant clearance and hepatic impairment and the safety profile in patients with mild hepatic impairment was similar to that seen in patients with no hepatic impairment. Safety and efficacy have not been evaluated in patients with moderate to severe hepatic impairment (see **PRECAUTIONS-Hepatic Impairment** and **DOSAGE AND ADMINISTRATION-Hepatic Impairment** sections).

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

Drug-Drug Interactions

There are no known drug-drug interactions. Fulvestrant does not significantly inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2C19, 2D6, and 3A4 *in vitro*, and studies of co-administration of fulvestrant with midazolam indicate that therapeutic doses of fulvestrant have no inhibitory effects on CYP 3A4 or alter blood levels of drug metabolized by that enzyme. Also, 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. Clinical studies of the effect of strong CYP 3A4 inhibitors on the pharmacokinetics of fulvestrant have not been performed.

Clinical Studies

Efficacy of FASLODEX was established by comparison to the selective aromatase inhibitor anastrozole in two randomized, controlled clinical trials (one conducted in North America, the other in Europe) 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 majority of patients in these trials had ER+ and/or PgR+ tumors. Patients who had ER-/PgR- or unknown disease must have shown prior response to endocrine therapy.

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. The North American trial was a double-blind, randomized trial in 400 postmenopausal women. The European trial was an open, randomized trial conducted in 451 patients. Patients on the FASLODEX arm of the North American trial received two separate injections (2 X 2.5 ml), whereas FASLODEX patients received a single injection (1 X 5 ml) in the European trial. 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.

The effectiveness endpoints were response rates (RR), based on the Union Internationale Contre le Cancer (UICC) criteria, and time to progression (TTP). Survival time was also determined. Confidence intervals (95.4%) were calculated for the difference in RR between the FASLODEX and anastrozole groups. The hazard ratio for an unfavorable event, (such as disease progression or death) between FASLODEX and anastrozole groups was also determined.

Table 2 provides the demographics and baseline characteristics of the postmenopausal

women randomized to FASLODEX 250 mg or anastrozole 1 mg.

TABLE 2: STUDY POPULATION DEMOGRAPHICS

Parameter	North American Trial		European Trial	
	FASLODEX 250 mg	Anastrozole 1 mg	FASLODEX 250 mg	Anastrozole 1 mg
No. of Participants	206	194	222	229
Median Age (yrs)	64	61	64	65
Age Range (yrs)	33 - 89	36 - 94	35 - 86	33 - 89
Receptor Status # (%)				
ER Positive	170 (83%)	156 (80%)	156 (70%)	173 (76%)
ER/PgR Positive	179 (87%)	169 (87%)	163 (73%)	183 (80%)
ER/PgR Unknown	13 (6%)	15 (8%)	51 (23%)	37 (16%)
Previous Therapy				
Tamoxifen	196 (95%)	187 (96%)	215 (97%)	225 (98%)
Adjuvant antiestrogen only	94 (46%)	94 (48%)	95 (43%)	100 (44%)
Antiestrogen for advanced disease +/- adjuvant use	110 (53%)	97 (50%)	126 (57%)	129 (56%)
Cytotoxic Chemotherapy	129 (63%)	122 (63%)	94 (42%)	98 (43%)
Site of Metastases				
Visceral only *	39 (19%)	45 (23%)	30 (14%)	41 (18%)
Viscera				
Liver involvement	47 (23%)	45 (23%)	48 (22%)	56 (24%)
Lung involvement	63 (31%)	60 (31%)	56 (25%)	60 (26%)
Bone only	47 (23%)	43 (22%)	38 (17%)	40 (17%)
Soft Tissue only	12 (6%)	13 (7%)	11 (5%)	8 (3%)
Skin and soft tissue	43 (21%)	41 (21%)	40 (18%)	35 (15%)

*Defined as liver or lung metastatic, or recurrent, disease

ER/PgR Positive defined as ER positive or PgR positive

ER/PgR Unknown defined as ER unknown and PgR unknown

Results of the trials, after a minimum follow-up duration of 14.6 months, are summarized in Table 3. The effectiveness of FASLODEX 250 mg was determined by comparing RR and TTP results to anastrozole 1 mg, the active control. With respect to response rate, the two studies ruled out (by one-sided 97.7% confidence limit) inferiority of FASLODEX to anastrozole of 6.3% and 1.4%.

Table 3: Efficacy Results

End point	North American Trial		European Trial	
	FASLODEX 250 mg (n=206)	Anastrozole 1 mg (n=194)	FASLODEX 250 mg (n=222)	Anastrozole 1 mg (n=229)
Objective tumor response Number (%) of subjects with CR + 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 (-1.44, 14.8)
Stable Disease for \geq 24 weeks (%)	26.7	19.1	24.3	30.1
Time to progression (TTP) Median TTP (days) Hazard ratio (FAS/ANA) 2-sided 95.4% CI	165	103 0.9 (0.7 to 1.1)	166	156 1.0 (0.8 to 1.26)
Survival Time Died n (%) Median Survival (days) Hazard Ratio 2-sided 95% CI	109 (52.9%) 837	92 (47.4%) 901 1.1 (0.8, 1.5)	125 (56.3%) 803	130 (56.8%) 742 1.0 (0.8, 1.3)

CR = Complete Response; PR = Partial Response; CI = Confidence Interval;
FAS = FASLODEX; ANA = anastrozole

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).

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.

CONTRAINDICATIONS

FASLODEX is contraindicated in pregnant women, and in patients with a known hypersensitivity to the drug or to any of its components.

WARNINGS

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 and has been shown to cross the placenta following single intramuscular doses in rats and in rabbits. In studies in the pregnant rat, intramuscular doses of fulvestrant 100 times lower than the maximum recommended human dose (based on body surface area [BSA]), caused an increased incidence of fetal abnormalities and death. Similarly, rabbits failed to maintain pregnancy and the fetuses showed an increased incidence of skeletal variations when fulvestrant was administered at one-half the recommended human dose (based on BSA).

There are no studies in pregnant women using 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, or potential risk for loss of the pregnancy. See **Pregnancy** section of **PRECAUTIONS**.

Because FASLODEX is administered intramuscularly, it should not be used in patients with bleeding diatheses, thrombocytopenia or patients on anticoagulants.

PRECAUTIONS

General

Before starting treatment with FASLODEX, pregnancy must be excluded (see **WARNINGS**).

Hepatic Impairment

Safety and efficacy have not been evaluated in patients with moderate to severe hepatic impairment (see **CLINICAL PHARMACOLOGY-Hepatic Impairment** and **DOSAGE AND ADMINISTRATION-Hepatic Impairment** sections).

Drug Interactions

Fulvestrant is metabolized by CYP 3A4 *in vitro*. Clinical studies of the effect of strong CYP 3A4 inhibitors on the pharmacokinetics of fulvestrant have not been performed (see **CLINICAL PHARMACOLOGY-Drug-Drug Interactions**).

Carcinogenesis, Mutagenesis and 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 approximately 1-, 3-, and 5-fold (in females) and 1.3-, 1.3-, and 1.6-fold (in males) the systemic exposure [AUC_{0-30 days}] achieved in women receiving the recommended dose of 250 mg/month. An increased incidence of benign ovarian granulosa cell tumors and testicular Leydig cell tumors was evident, in females dosed at 10 mg/rat/15 days and males dosed at 15 mg/rat/30 days, respectively. Induction of such tumors is consistent with the pharmacology-related endocrine feedback alterations in gonadotropin levels caused by an antiestrogen.

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

In female rats, fulvestrant administered at doses ≥ 0.01 mg/kg/day (approximately one-hundredth of the human recommended dose based on body surface area [BSA], for 2 weeks prior to and for 1 week following mating, caused a reduction in fertility and embryonic survival. No adverse effects on female fertility and embryonic survival were evident in female animals dosed at 0.001 mg/kg/day (approximately one-thousandth of the human dose based on BSA). Restoration of female fertility to values similar to controls was evident following a 29-day withdrawal period after dosing at 2 mg/kg/day (twice the human dose based on BSA). The effects of fulvestrant on the fertility of female rats appear to be consistent with its anti-estrogenic activity. The potential effects of fulvestrant on the fertility of male animals were not studied but in a 6-month toxicology study, male rats treated with intramuscular doses of 15 mg/kg/30 days, 10 mg/rat/30 days, or 10 mg/rat/15 days fulvestrant showed a loss of spermatozoa from the seminiferous tubules, seminiferous tubular atrophy, and degenerative changes in the epididymides. Changes in the testes and epididymides had not recovered 20 weeks after cessation of dosing. These fulvestrant doses correspond to approximately 2-, 3-, and 3-fold the systemic exposure [$AUC_{0-30 \text{ days}}$] achieved in women.

Pregnancy

Pregnancy Category D: (See WARNINGS).

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

Nursing Mothers

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

Pediatric Use

The safety and efficacy of FASLODEX in pediatric patients have not been established.

Geriatric Use

When tumor response was considered by age, objective responses were seen in 24% and 22% of patients under 65 years of age and in 16% and 11% of patients 65 years of age and older, who were treated with FASLODEX in the European and North American trials, respectively.

ADVERSE REACTIONS

The most commonly reported adverse experiences 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 flushes), and pharyngitis.

Injection site reactions with mild transient pain and inflammation were seen with FASLODEX and occurred in 8.7% of patients (1% of treatments) given the single 5 mL injection (European Trial) and in 27% of patients (4.6% of treatments) given the 2 x 2.5 mL injections (North American Trial).

Table 4 lists adverse experiences 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 4: Combined Trials Adverse Events $\geq 5\%$

Body system and adverse event^a	FASLODEX 250 mg N=423 (%)	Anastrozole 1 mg N=423 (%)
Body as a whole	68.3	67.6
Asthenia	22.7	27.0
Pain	18.9	20.3
Headache	15.4	16.8
Back pain	14.4	13.2
Abdominal pain	11.8	11.6
Injection site pain*	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

Body system and adverse event ^a	Fulvestrant 250 mg N=423 n (%)	Anastrozole 1 mg N=423 n (%)
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

^aA patient may have more than one adverse event.

*All patients on FASLODEX received injections, but only those anastrozole patients who were in the North American study received placebo injections.

Other adverse events reported as drug-related and seen infrequently (<1%) include thromboembolic phenomena, myalgia, vertigo, and leukopenia.

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.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Adults (including the elderly): The recommended dose is 250 mg to be administered intramuscularly into the buttock at intervals of one month as either a single 5 mL injection or two concurrent 2.5 mL injections (see **HOW SUPPLIED**). The injection should be administered slowly.

Patients with Hepatic Impairment

FASLODEX has not been studied in patients with moderate or severe hepatic compromise. No dosage adjustment is recommended in patients with mild hepatic impairment (see **CLINICAL PHARMACOLOGY-Hepatic Impairment** and **PRECAUTIONS-Hepatic Impairment** sections).

Instructions for Intramuscular use, handling and disposal

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

For the 2 x 2.5 mL syringe package only, both syringes must be administered to receive the 250 mg recommended monthly 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™

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.

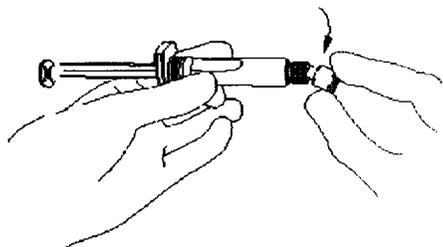
Activation of the protective mechanism may cause minimal splatter of fluid that may remain on the needle after injection.

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

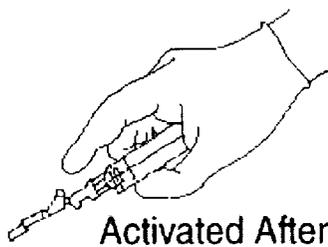
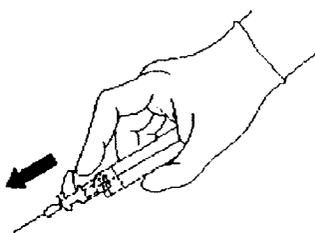
After single use, discard in an approved sharps collector in accordance with applicable regulations and institutional policy.

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

Faslodex
Figure 1



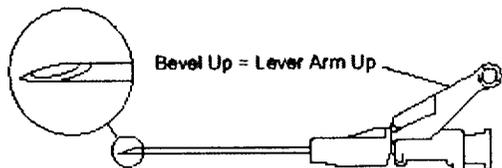
Faslodex
Figure 2



Activated After Use

Faslodex

Figure 3



HOW SUPPLIED

One 5 mL clear neutral glass (Type 1) barrel containing 5 mL (50 mg/mL) FASLODEX Injection for intramuscular injection and fitted with a tamper evident closure.

NDC 0310-0720-50 5 mL Prefilled Syringes

Two 5 mL clear neutral glass (Type 1) barrels, each containing 2.5 mL (50 mg/mL) of FASLODEX Injection for intramuscular injection and fitted with a tamper-evident closure.

NDC 0310-0720-25 Two 5 mL Prefilled Syringes containing 2.5 mL

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

Storage

Store in a refrigerator, 2°-8°C (36°F -46°F). Store in original container.

Distributed by:

AstraZeneca Pharmaceuticals LP

Wilmington, DE 19850

Manufactured for:

IPR Pharmaceuticals Inc.

Carolina, PR

by:

Vetter Pharma-Fertigung GMBH & Co. KG

Ravensburg, Germany

Made in Germany

Rev 04/25/02



Two pre-filled
syringes
containing
2.5mL



For Single-Patient Use Only

NDC 0310-0720-25



250 mg (50 mg/mL)

Two Pre-filled Syringes each containing 2.5mL of 125 mg
fulvestrant (50 mg/mL)

For Intramuscular Use Only

Rx only



Two pre-filled syringes
containing 2.5mL

USUAL DOSAGE: See Prescribing Information for details of administration. See below for assembly instructions.
STORAGE: Refrigerate, 2-8°C (36-46°F). Store in the original package.

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

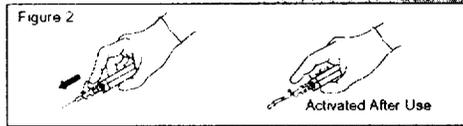
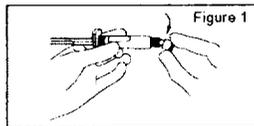
Carton contains: Two 5mL pre-filled syringes containing 2.5mL or 125 mg of FASLODEX™ (50 mg/mL), Sterile prep pad and 2 SafetyGlide™ shielding IM injection needles.

PLEASE NOTE: The syringes are supplied half full. Both syringes must be administered to receive the 250 mg recommended monthly dose.

FASLODEX™ also contains: Alcohol (96%), Benzyl alcohol, Benzyl Benzoate, and Castor Oil.

INSTRUCTIONS FOR USE:

1. Remove glass syringe barrel from tray and check that it is not damaged.
2. Peel open the SafetyGlide™ outer packaging.
3. Break the seal of the white plastic cover on the syringe luer connector to remove the cover with the attached rubber lip cap (see Figure 1).
4. Twist to lock the needle to the luer connector.
5. Remove needle sheath.
6. Remove excess gas from the syringe (a small gas bubble may remain).
7. Administer intramuscularly in the gluteus.
8. Immediately activate needle protection after withdrawal from patient by pulling the plunger completely forward until needle is fully extended (see Figure 2).
9. Visually confirm that the needle is fully advanced and the needle is fully extended. Activate, discard immediately into an approved sharps collector. For complete SafetyGlide™ instructions, see prescribing information.



Two pre-filled
syringes
containing
2.5mL
FASLODEX™
fulvestrant
injection

XXXXXX
XXXXXX
XXXXXX
LOT
EXP

FASLODEX™
fulvestrant
injection

SafetyGlide™ is a trademark of Becton Dickinson and Company. All other trademarks are the property of the AstraZeneca group. © AstraZeneca 2011

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AstraZeneca Pharmaceuticals LP, Wilmington, NC
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By: Vetter Pharma-Fertigung GmbH & Co. KG
Ravensburg, Germany Made in Germany

DRAFT
Faslodex 2.5mL Syringe Label

NDC 0310-0720-25

 **FASLODEX**[™]
fulvestrant
injection

125 mg (50 mg/mL) / 2.5mL

For Intramuscular Use Only

Both syringes must be administered to receive
the 250 mg recommended monthly dose

AstraZeneca

XXXXXX
Variable Data

XXXXXX
Variable Data

DRAFT
Faslodex 5mL Carton

FASLODEX[™]
fulvestrant
injection

One 5mL
pre-filled
syringe



For Single-Patient Use Only

FASLODEX[™]
fulvestrant
injection

250 mg (50 mg/mL)

For Intramuscular Use Only

Rx only

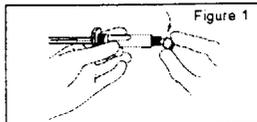
AstraZeneca

USUAL DOSAGE: See Prescribing Information for details of administration. See bottom of carton for assembly instructions.
STORAGE: Refrigerate, 2-8°C (36-46°F). Store in the original package.
WARNING: As with all medications, keep out of the reach of children.

LOT
EXP

INSTRUCTIONS FOR USE:

1. Remove glass syringe barrel from tray and check that it is not damaged.
2. Peel open the SafetyGlide[™] outer packaging.
3. 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).
4. Twist to lock the needle to the luer connector.
5. Remove needle sheath.
6. Remove excess gas from the syringe (a small gas bubble may remain).



7. Administer intramuscularly in the buttock.
 8. Immediately activate needle protection device upon withdrawal from patient by pushing lever arm completely forward until needle tip is fully covered (see Figure 2).
 9. 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.
- For complete SafetyGlide[™] instruction refer to prescribing information.



Carton contains: One 5mL pre-filled syringe, sterile alcohol swabs, and needle shielding (injection).
FASLODEX[™] also contains benzyl alcohol, Benzyl Benzoate, and Chlorobutol.

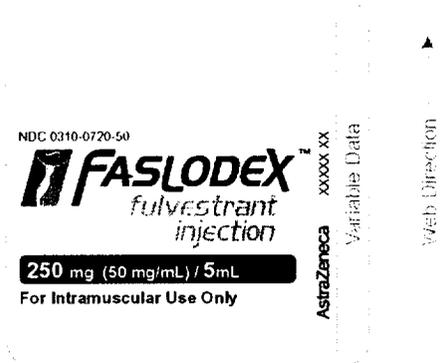
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XXXXXX
XXXXXX
XXXXXX

FASLODEX[™] One 5mL
pre-filled
syringe
fulvestrant
injection

FASLODEX[™] One 5mL
pre-filled
syringe
fulvestrant
injection

DRAFT
Faslodex 5mL Syringe Label



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

/s/

Robert Temple

4/25/02 02:20:43 PM

39 pages redacted from this section of
the approval package consisted of draft labeling