

PRODUCT MONOGRAPH

 FASLODEX[®]

fulvestrant injection

50 mg/mL

Nonagonist Estrogen Receptor Antagonist

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Pr FASLODEX[®]

fulvestrant injection
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular injection	Pre-filled syringe injection 50 mg/mL	Ethanol 96%, benzyl alcohol, benzyl benzoate, castor oil

INDICATIONS AND CLINICAL USE

FASLODEX[®] (fulvestrant) is indicated for the hormonal treatment of locally advanced or metastatic breast cancer in postmenopausal women, regardless of age, who have disease progression following prior anti-estrogen therapy.

Geriatrics:

No changes in dose are necessary for elderly patients.

Pediatrics:

FASLODEX is not recommended for use in the pediatric population, as safety and efficacy have not been established in this age group.

CONTRAINDICATIONS

- Patients with known hypersensitivity to fulvestrant or to any of the excipients. For a complete listing of ingredients, see the Dosage Forms, Composition and Packaging section of the Product Monograph.
- Pregnant or lactating women.

WARNINGS AND PRECAUTIONS

Body as a Whole

FASLODEX (fulvestrant) is unlikely to impair the ability of patients to drive or operate machinery. However, during treatment with FASLODEX, asthenia has been reported, and caution should be observed by those patients who experience this symptom when driving or operating machinery.

Hematologic

Due to the route of administration (intramuscular injection), caution should be used before treating patients on anticoagulants or patients with bleeding diatheses or thrombocytopenia.

Hepatic

Fulvestrant is metabolized primarily in the liver; thus, clearance may be reduced in subjects with hepatic impairment. Pharmacokinetic data show that the mean clearance is reduced 2.2 fold in subjects with moderate hepatic impairment in comparison to healthy subjects. The average AUC of fulvestrant in these subjects (Child-Pugh Category B) increased by approximately 70% compared to patients with normal hepatic function (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency). There are no efficacy and safety data available for FASLODEX in breast cancer patients with hepatic impairment.

Caution should be used with FASLODEX in patients with mild to moderate hepatic impairment. The potential risk/benefit to patients with moderate hepatic impairment should be carefully considered before administration of FASLODEX. FASLODEX has not been investigated in subjects with severe (Child-Pugh Category C) hepatic impairment; therefore, it is not recommended for use in these patients.

Immune

Hypersensitivity reactions including angioedema and urticaria may occur. These reactions may occur shortly after injection, or in one reported case of angioedema, several days after injection. Local injection site reactions (e.g. pruritus, urticaria) may occur even after prior uneventful injections, and have been reported to develop with time into a systemic allergic response (e.g. widespread urticaria). FASLODEX therapy may need to be discontinued.

Musculoskeletal

There are no long-term data on the effect of fulvestrant on bone. Due to the mode of action of fulvestrant, there is a potential risk of osteoporosis.

Renal

Caution should be used before treating patients with creatinine clearance less than 30 mL/min.

Special Populations

Pregnant Women: FASLODEX is contraindicated in pregnant women.

FASLODEX can cause fetal harm if administered to a pregnant woman. Women of childbearing potential should be advised not to become pregnant while receiving FASLODEX.

If a patient becomes pregnant while receiving FASLODEX she should be apprised of the potential hazard to the fetus, or the potential risk for loss of pregnancy.

Nursing Women: FASLODEX is contraindicated in lactating women.

FASLODEX is found in rats' milk at levels significantly higher than those in rat plasma. It is not known if fulvestrant is excreted in human milk. However, since 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.

Pediatrics: FASLODEX is not recommended for use in the pediatric population, as safety and efficacy have not been established in this age group.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

FASLODEX (fulvestrant) 500 mg was well tolerated with a similar tolerability profile to FASLODEX 250 mg. Adverse drug reactions for which there is evidence of an increased incidence for FASLODEX 500 mg include injection site reactions and hypersensitivity reactions (predominantly pruritus). An increased incidence of injection site reactions and hypersensitivity reactions, such as pruritus, is consistent with the increased number of injections required for the FASLODEX 500 mg dose regimen compared to FASLODEX 250 mg.

Following review of clinical trial data, a number of adverse drug reactions (ADRs) were identified for FASLODEX 500 mg, where a causal link has been established between the ADR and FASLODEX treatment. These ADRs were assigned to frequency categories based on incidences of similar preferred terms (PTs) for adverse events (AEs) using medical dictionary for regulatory activities (MedDRA). The frequencies are based on all reported AEs regardless of the investigator assessment of causality. The following ADRs were identified as being very common (incidence rate >10%): Injection site reactions, asthenia, elevated liver enzymes (ALT, AST, ALP) and nausea. Common ADRs (incidence rate >1% but ≤10%) were: hot flushes, headache, vomiting, diarrhoea, anorexia, rash, urinary tract infection and hypersensitivity reactions.

Serious adverse events (SAEs; irrespective of causality) were typically reported at single incidences in FASLODEX 500 mg clinical trials for any given MedDRA PT. At the system organ class (SOC) level, the highest incidence of SAEs was reported in the infections and infestations SOC (incidence = 1.8%).

AEs leading to permanent discontinuation of treatment (DAEs; irrespective of causality) were typically reported at single incidences in FALSODEX 500 mg clinical trials for any given MedDRA PT. At the SOC level, the highest incidence of DAEs was reported in the nervous system disorders category (incidence = 0.5%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Safety data from the following studies were integrated for the evaluation of safety: a randomised, double-blind, parallel-group, multicentre, Phase III study (CONFIRM), a randomised, open-label, multicentre, Phase II study (NEWEST), and 2 randomised, double-blind, parallel-group, multicentre, Phase II studies (FINDER1 [Japanese patients only] and FINDER2). The data that were pooled were those available with consideration given to individual study design features such as timing of assessments. This pooled analysis of safety included data from 560 patients treated with fulvestrant 500 mg (mean exposure: 261.89 days) and 567 patients treated with fulvestrant 250 mg (mean exposure: 218.43 days). The FINDER1 and FINDER2 studies included fulvestrant 250 mg + loading dose treatment groups; the data from these patients were not included in the pooled analysis of safety as they are not relevant to the fulvestrant 500 mg vs fulvestrant 250 mg comparison.

In each study, conventional methodology was used for the assessment of the safety and tolerability of fulvestrant 500 mg, including the reporting of AEs (irrespective of causality or seriousness), treatment-related AEs as judged by the investigator, and clinical laboratory data. Any detrimental change in a patient's medical condition was considered to be an AE unless this was clearly attributable to breast cancer progression. Consequently, these safety data include AEs that would be expected in patients with advanced breast cancer and may also include the sequelae of prior or concomitant treatment. AEs were coded using MedDRA PTs.

The most common adverse events for FASLODEX 500 mg and FASLODEX 250 mg treatment arms from one Phase III and three Phase II trials are presented in Table 1.

In the pooled Phase II and Phase III safety database, the most frequently reported adverse event was injection site pain with 13.9% vs. 10.2% of patients in the FASLODEX 500 mg and 250 mg groups, respectively. This was followed by nausea, fatigue, hot flush and headache with 10.2% vs. 13.9%, 9.6% vs. 7.1%, 8.8% vs. 8.6% and 8.0% vs. 7.2%, respectively, in the 500 mg and 250 mg groups, respectively. The proportion of patients who reported at least 1 adverse event in each group was similar with 70.2% vs. 68.3% in the FASLODEX 500 mg vs. 250 mg groups, respectively.

Table 1 Adverse events in the FASLODEX 500 mg and FASLODEX 250 mg treatment arms in pooled^a data that includes CONFIRM (Phase III) and three Phase II trials (incidence \geq 5% in either pooled group)

MedDRA preferred term ^b	Number (%) of patients, by treatment	
	FASLODEX 500 mg	FASLODEX 250 mg
	Pooled ^a	Pooled ^a
	500 mg (N=560)	250 mg (N=567)
Patients with any AE	393 (70.2)	387 (68.3)
Gastrointestinal Disorders		
Nausea	57 (10.2)	79 (13.9)
Vomiting	33 (5.9)	32 (5.6)
Diarrhea	30 (5.4)	24 (4.2)
General Disorders and Administration Site Conditions		
Injection site pain	78 (13.9)	58 (10.2)
Fatigue	54 (9.6)	40 (7.1)
Asthenia	29 (5.2)	31 (5.5)
Infections and Infestations		
Nasopharyngitis	24 (4.3)	33 (5.8)
Metabolism and Nutrition Disorders		
Anorexia	32 (5.7)	20 (3.5)
Musculoskeletal and Connective Tissue Disorders		
Back pain	40 (7.1)	54 (9.5)
Arthralgia	38 (6.8)	36 (6.3)
Bone pain	37 (6.6)	30 (5.3)
Pain in extremity ^c	32 (5.7)	38 (6.7)
Nervous system Disorders		
Headache	45 (8.0)	41 (7.2)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	31 (5.5)	32 (5.6)
Vascular Disorders		
Hot flush	49 (8.8)	49 (8.6)
Hypertension	24 (4.3)	29 (5.1)

^a Pooled data: CONFIRM, NEWEST, FINDER1 and FINDER2.

^b Patients with multiple occurrences of the same event were counted only once per event.

^c Following data queries to the investigational sites, it was confirmed that pain in extremity was not linked to injection site pain but was a distinct and separate AE.

The organ system class is presented alphabetically and the preferred-terms are presented in order of decreasing frequency for the pooled data in the 500 mg group.

MedDRA : Medical Dictionary for Regulatory Activities.

Based on the known pharmacological and safety profile of FASLODEX, and potential safety issues for hormonal therapies, the pre-specified categories of adverse events listed in Table 2 were selected for evaluation in the CONFIRM trial.

Table 2 **Number of patients experiencing pre-specified adverse events in the CONFIRM trial**

Pre-specified event	Number (%) of patients		
	FASLODEX 500 mg (N=361)	FASLODEX 250 mg (N=374)	p-value
GI disturbances	73 (20.2)	76 (20.3)	1.000
Joint disorders	68 (18.8)	70 (18.7)	1.000
Injection site reactions	49 (13.6)	50 (13.4)	1.000
Hot flushes	30 (8.3)	23 (6.1)	0.318
Urinary tract infection	8 (2.2)	8 (2.1)	1.000
Ischaemic cardiovascular disorders	5 (1.4)	7 (1.9)	0.773
Thromboembolic events	3 (0.8)	6 (1.6)	0.506
Vaginitis	3 (0.8)	1 (0.3)	0.366
Weight gain	1 (0.3)	1 (0.3)	1.000
Osteoporosis	1 (0.3)	0	0.492
Endometrial dysplasia	0	0	NC

NC= Not Calculable

Table 3 lists adverse events reported with an incidence of $\geq 5\%$ in the two randomised controlled trials 9238IL/0020 and 9238IL/0021, regardless of causality, during treatment or the specified safety follow-up period (defined as 8 weeks after the last injection or 30 days after ingestion of the last tablet). Both trials (9238IL/0020 and 9238IL/0021) were conducted in postmenopausal (naturally and artificially induced) women with locally advanced or metastatic breast cancer who had disease progression following anti-estrogen or progestin therapy for either advanced or early breast cancer.

Table 3 Adverse events occurring at an incidence of $\geq 5\%$ (irrespective of causality): Combined results from Trials 9238IL/0020 and 9238IL/0021

Body System and Adverse Event^a	FASLODEX 250mg (IM injection/month) N=423 (%)	Anastrozole 1 mg (oral tablet/day) 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
Vasodilation	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

Body System and Adverse Event^a	FASLODEX 250mg (IM injection/month) N=423 (%)	Anastrozole 1 mg (oral tablet/day) N=423 (%)
Bone Pain	15.8	13.7
Arthritis	2.8	6.1
Nervous System	34.3	33.8
Dizziness	6.9	6.6
Insomnia	6.9	8.5
Paresthesia	6.4	7.6
Depression	5.7	6.9
Anxiety	5.0	3.8
Respiratory System	38.5	33.6
Pharyngitis	16.1	11.6
Dyspnea	14.9	12.3
Cough increased	10.4	10.4
Skin and Appendages	22.2	23.4
Rash	7.3	8.0
Sweating	5.0	5.2
Urogenital System	18.2	14.9
Urinary tract infection	6.1	3.5

^a A patient may have more than one adverse event

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

DRUG INTERACTIONS

Overview

FASLODEX (fulvestrant) does not significantly inhibit any of the major cytochrome P₄₅₀ (CYP) isoenzymes *in vitro*, and results from a clinical pharmacokinetic trial in 8 healthy males involving co-administration of fulvestrant (36 mg intramuscularly) with midazolam (7.5 mg p.o.) also suggest that therapeutic doses of fulvestrant will have no inhibitory effects on CYP3A4. In addition, although fulvestrant can be metabolised by CYP3A4 *in vitro*, a clinical study in 8 healthy males with rifampicin (600 mg p.o.), an inducer of CYP3A4, showed no change in the pharmacokinetics of a 10 mg IV dose of fulvestrant as a result of the induction of CYP3A4. Results from a clinical study in 18 healthy subjects (17 male, 1 female) with ketoconazole (400 mg daily), a potent inhibitor of CYP3A4, also indicated that there is no

clinically relevant change in the pharmacokinetics of an 8 mg IV dose of fulvestrant. Dosage adjustment is not necessary in patients co-prescribed CYP3A4 inhibitors or inducers.

Drug-Drug Interactions

There are no known drug-drug interactions requiring dose adjustment.

Drug-Food Interactions

Interactions with particular foods have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Adult Females: The recommended dose regimen of FASLODEX (fulvestrant) is 500 mg to be administered intramuscularly as two 5 mL (250 mg/5 mL) injections, one in each buttock. The recommended dosing schedule is as follows: FASLODEX 500 mg dose to be administered on days 0, 14, 28 and then every 28 days thereafter. It is recommended that the injection be administered slowly

Patients with hepatic insufficiency: No dose adjustments are recommended for patients with mild or moderate (Child Pugh Category A and B) hepatic impairment. However, as the clearance of fulvestrant may be decreased in patients with hepatic impairment, these patients should be monitored for side effects when treated with fulvestrant (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency). The use of fulvestrant has not been evaluated in patients or pharmacokinetic study subjects with severe (Child-Pugh Category C) hepatic impairment; therefore, it is not recommended for use in these patients.

Patients with renal insufficiency: No dose adjustments are recommended for patients with a creatinine clearance greater than 30 mL/min. Safety and efficacy have not been evaluated in patients with creatinine clearance less than 30 mL/min.

Elderly: No dose adjustment is required for elderly patients.

Children: Not recommended for use in children or adolescents, as safety and efficacy have not been established in this age group.

Administration

Instructions for use, handling and disposal

Warning- Do not autoclave safety needle (BD SafetyGlide™ Shielding Hypodermic Needle) before use. Hands must remain behind the needle at all times during use and disposal.

For each syringe:

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

Break the seal of the white plastic cover on the syringe Luer connector Luer-Lok to remove the cover with the attached rubber tip cap (see Figure 1).

Figure 1

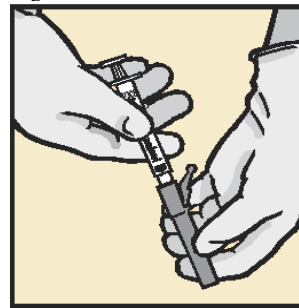


Twist to lock the needle to the Luer connector.

Peel open the safety needle (SafetyGlide™) outer packaging.

Attach the safety needle to the Luer-Lok (see Figure 2)

Figure 2



Twist until firmly seated.

Pull shield straight off needle to avoid damaging needle point.

Transport filled syringe to point of administration.

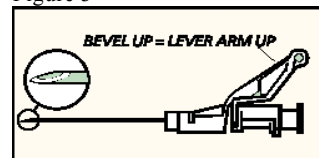
Remove needle sheath.

Parenteral solutions must be inspected visually for particulate matter and discoloration prior to administration.

Expel excess gas from the syringe.

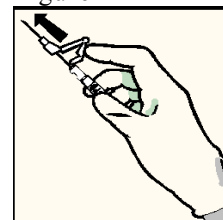
Administer intramuscularly slowly (1-2 minutes/injection) into the buttock. For user convenience, the needle bevel- up position is oriented to the lever arm (see Figure 3).

Figure 3



After injection, immediately apply a single-finger stroke to the activation assisted lever arm to activate the shielding mechanism (see Figure 4).

Figure 4



SafetyGlide™ instructions are from Becton Dickinson

BD SafetyGlide™ is a trademark of Becton Dickinson and Company.

Reorder number 305917.

OVERDOSAGE

For management of suspected drug overdose, contact your regional Poison Control Centre.

There is no clinical experience of overdose with FASLODEX (fulvestrant) in humans. Animal studies have shown no adverse effects with intramuscular doses of greater than 400-fold of the clinical dose. Further animal studies, in which fulvestrant was dosed either monthly or twice monthly and achieved plasma levels several-fold higher than those seen in humans, showed no effects other than those related directly or indirectly to antiestrogen activity.

If overdose occurs, this should be managed symptomatically.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

FASLODEX (fulvestrant) is an estrogen receptor (ER) antagonist that has a mode of action leading to downregulation of ER protein. Fulvestrant is a nonagonist ER antagonist that blocks the trophic actions of estrogens without itself having any partial agonist (estrogen-like) activity. Fulvestrant binds to estrogen receptors in a competitive manner with an affinity comparable to that of estradiol.

Fulvestrant is a reversible inhibitor of the growth of estrogen-sensitive human breast cancer cells *in vitro*. Fulvestrant inhibits the growth of estrogen-sensitive human breast cancer xenografts in nude mice, prevents the establishment of tumours from xenografts of human breast cancer cells, and suppresses the growth of breast tumours. Furthermore, fulvestrant inhibits the growth of tamoxifen-resistant breast cancer cells *in vitro* and of tamoxifen-resistant breast tumours *in vivo*. Fulvestrant resistant breast tumours may also be cross-resistant to tamoxifen.

Pharmacodynamics

A clinical trial in postmenopausal women with primary breast cancer has shown that a single 250 mg dose of fulvestrant significantly downregulates ER expression in ER positive tumours, when compared to placebo. This same study also showed for fulvestrant a significant decrease in progesterone receptor (PgR) expression compared to placebo after 15 - 22 days of treatment. These data are consistent with fulvestrant having no agonist activity.

A trial in healthy postmenopausal volunteers showed that, compared to placebo, pre-treatment with 250 mg fulvestrant resulted in significantly reduced stimulation of the postmenopausal endometrium in volunteers treated with 20 mcg per day ethinyl estradiol. Mean endometrial thickness after treatment with 250 mg fulvestrant was 4.2 mm, and with placebo it was 11.22 mm.

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. The reduction in levels of sex hormone-binding globulin indicates a lack of agonist properties.

Pharmacokinetics

Following intravenous or intramuscular administration, fulvestrant is rapidly cleared at a rate approximating the hepatic blood flow (nominally 10.5 mL plasma/min/kg). FASLODEX (fulvestrant) long-acting intramuscular injection maintains plasma fulvestrant concentrations within a range of up to 3-fold difference between peak and trough concentrations over a period of at least 28±3 days after injection. Administration of FASLODEX 500 mg achieves exposure levels at or close to steady state within the 1st month of dosing (see Table 4).

Results from single-dose studies of fulvestrant are predictive of multiple-dose pharmacokinetics.

Table 4 Summary of fulvestrant pharmacokinetic parameters [gMean (CV%)] in postmenopausal advanced breast cancer patients after intramuscular administration of the fulvestrant 500 mg dosing regimen

		C_{max} (ng/mL)	C_{min} (ng/mL)	AUC (ng.hr/mL)
Fulvestrant 500 mg	Single dose*	25.1(35.3)	16.3(25.9)	11400 (33.4)
	Multiple dose steady state**	28.0(27.9)	12.2(21.7)	13100(23.4)

* Month 1 of the dosing regimen (ie, Day 0, 14 and 28)

** Month 3

Absorption: Fulvestrant is not administered orally.

Distribution: Fulvestrant is subject to extensive and rapid distribution; the apparent volume of distribution at steady state is large (approximately 3 to 5 L/kg), which suggests that the compound 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. No studies were conducted on drug-drug competitive protein binding interactions, as most reported interactions of this type involved binding to albumin and α -1-acid-glycoproteins.

Metabolism: Biotransformation and disposition of fulvestrant in humans have been determined following intramuscular and intravenous administration of ¹⁴C-labelled 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, and 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. The metabolism of fulvestrant in humans yields a similar profile of metabolites to that found in

other species. 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 CYP3A4 is the only P₄₅₀ isoenzyme involved in the oxidation of fulvestrant. However, the relative contribution of P₄₅₀ and non-P₄₅₀ routes *in vivo* is unknown.

Excretion: Fulvestrant is rapidly cleared by the hepatobiliary route with the overall rate of elimination being determined by the mode of administration, i.e., with monthly administration of FASLODEX long acting intramuscular formulation, exposure, and hence elimination, is primarily determined by the rate of release from the injection site. Excretion is primarily via the feces (approximately 90%). Renal elimination of drug-related material is negligible (less than 1%).

Special Populations and Conditions

Geriatrics: No difference in the fulvestrant pharmacokinetic profile was detected with regard to age (range 33 to 89 years).

Gender: Following administration of a single intravenous dose, there were no pharmacokinetic differences between men and either premenopausal or 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 discernible differences in fulvestrant plasma pharmacokinetics were observed among these groups. In a separate trial, pharmacokinetic data from postmenopausal Japanese women living in Japan were comparable to those obtained in non-Japanese patients.

Hepatic Insufficiency: FASLODEX is metabolized primarily in the liver.

The pharmacokinetics of fulvestrant has been evaluated in a single-dose clinical trial conducted in 21 subjects (7 subjects with Child-Pugh Category A and 7 with Category B hepatic impairment due to cirrhosis, 7 healthy subjects), using a high dose (100 mg) of a shorter duration intramuscular injection formulation. There was a 1.3 and 2.2-fold reduction in mean clearance in subjects with Child-Pugh Category A and B hepatic impairment, respectively, compared to healthy subjects. Subjects with mild hepatic impairment (Child-Pugh Category A) had comparable mean AUC to those with normal hepatic function, while subjects with moderate hepatic impairment (Child-Pugh Category B) had an increase of approximately 70% in average AUC compared to patients with normal hepatic function. Child-Pugh Category C subjects were not evaluated; it is expected that clearance would be further reduced in this group of subjects.

Modelled intramuscular mean steady state plasma concentrations of fulvestrant in subjects with Child-Pugh Category A and B hepatic impairment fall within the upper 95% confidence limit of the mean steady state concentrations expected for patients with normal hepatic function given the intramuscular formulation. Given the known safety profile of fulvestrant,

no dose adjustment is considered to be necessary in patients with Child-Pugh Category A or B hepatic impairment, although they should be monitored for side effects. Fulvestrant is not recommended for use in patients with severe (Child-Pugh Category C) hepatic impairment.

STORAGE AND STABILITY

Store refrigerated at 2 to 8°C. Store in original package.
Single dose syringe. Discard unused portion.

DOSAGE FORMS, COMPOSITION AND PACKAGING

FASLODEX (fulvestrant) solution for injection is a clear, colourless to yellow, viscous liquid. In addition to the active ingredient fulvestrant, each pre-filled syringe contains the following inactive ingredients: ethanol 96%, benzyl alcohol, benzyl benzoate, and castor oil.

FASLODEX is available in a package of two 250 mg/5 mL (50 mg/mL) pre-filled syringes. Each syringe is presented in a tray with polystyrene plunger rod and a safety needle (SafetyGlide™) for connection to the barrel.

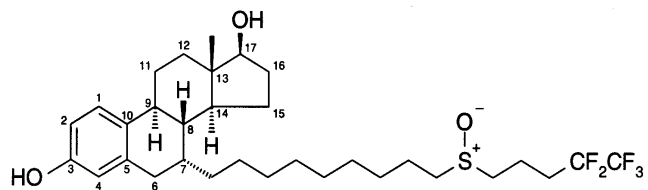
As with all parenteral drug products, syringes should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name:	fulvestrant
Chemical Name:	7 α -[9-(4,4,5,5,5-pentafluoropentylsulphinyl) nonyl]estra-1,3,5-(10)- triene-3,17 β -diol
Molecular Formula and Molecular Mass:	C ₃₂ H ₄₇ F ₅ O ₃ S and 606.8
Structural Formula:	



Physiochemical Properties:

The active ingredient fulvestrant is a white crystalline solid powder.

FASLODEX solution for injection is a clear, colourless to yellow, viscous liquid.

Fulvestrant has a very high lipophilicity and extremely low aqueous solubility. Fulvestrant is very soluble in alcohols (>200 mg/mL in benzyl alcohol and ethanol) and glycols (70 mg/mL in propylene glycol) and poorly soluble in fixed oils with the exception of castor oil in which solubility is 13 mg/mL.

CLINICAL TRIALS

There were no clinical trials conducted with FASLODEX (fulvestrant) in the premenopausal population. Some women of premenopausal age with advanced breast cancer were entered in FASLODEX clinical studies provided they met the protocol definition for postmenopausal status.

Efficacy of FASLODEX was established for FASLODEX 250 mg compared to anastrozole in clinical trials 9238IL/0020 and 9238IL/0021. The efficacy of FASLODEX 500 mg versus FASLODEX 250 mg was established in CONFIRM (Study D6997C00002).

Comparison of FASLODEX 250 mg and Anastrozole 1 mg

FASLODEX was studied in two randomised, controlled clinical trials [a North American study (9238IL/0021), and a predominantly European study (9238IL/0020)] in postmenopausal (naturally and artificially induced) women with locally advanced or metastatic breast cancer

who had disease progression following endocrine therapy (excluding aromatase inhibitors) for either advanced or early breast cancer. The majority of patients in these trials were ER+ and/or PgR+. Patients who had ER-/PgR- or unknown disease were required to have shown a prior response to endocrine therapy to be eligible to participate in the trials.

A total of 851 patients between the ages of 33 and 89 years old were randomised to receive trial treatment. These patients received either FASLODEX 250 mg intramuscularly once a month, or anastrozole 1 mg orally once a day. In addition, a total of 163 patients were randomised to a 125 mg per month dose, but an interim analysis showed a very low response rate and this low dose group was discontinued.

Table 5 provides the demographics and baseline characteristics of the postmenopausal women randomised in Trials 9238IL/0020 and 9238IL/0021.

Table 5 **Trials 9238IL/0020 and 9238IL/0021 - Demographics and baseline characteristics**

Parameter	North American Trial 9238IL/0021		European Trial 9238IL/0020	
	FASLODEX 250 mg	Anastrozole 1 mg	FASLODEX 250 mg	Anastrozole 1 mg
No. of Participants	206	194	222	229
Mean Age (yrs)	63	62	63	64
Age Range (yrs)	33 - 89	36 - 94	35 - 86	33 - 89
Hormone Receptor Status # (%)				
ER and/or PgR positive	179 (87%)	169 (87%)	163 (73%)	183 (80%)
ER/PgR negative ^a	14 (7%)	10 (5%)	8 (4%)	9 (4%)
ER and PgR unknown	13 (6%)	15 (8%)	51 (23%)	37 (16%)
Prior treatment				
Adjuvant endocrine ^b	122 (59%)	116 (60%)	121 (55%)	119 (52%)
Endocrine therapy for advanced disease	110 (53%)	97 (50%)	126 (57%)	129 (56%)
Cytotoxic chemotherapy	129 (63%)	122 (63%)	94 (42%)	98 (43%)
Extent of metastatic or recurrent disease at baseline				
Soft Tissue only	12 (6%)	13 (7%)	11 (5%)	8 (4%)
Bone only	47 (23%)	43 (22%)	38 (17%)	40 (18%)
Visceral only	39 (19%)	45 (23%)	30 (14%)	41 (18%)
Lymph node only	15 (7%)	17 (9%)	22 (10%)	21 (9%)
Not recorded	1 (1%)	2 (1%)	0	1 (0%)
Mixed*	92 (45%)	87 (45%)	121 (55%)	118 (52%)

^a ER/PgR negative is defined as ER negative and either PgR negative or PgR unknown

^b Adjuvant endocrine therapy included tamoxifen for >95% of patients

* Mixed is defined as breast and/or a combination of skin, bone, liver, lung, or lymph nodes

Trial results

The primary efficacy endpoint was time to progression; secondary endpoints included objective response, clinical benefit, time to treatment failure, quality of life and survival. Overall, FASLODEX was shown to be at least as effective as anastrozole in terms of time to progression, in a non-inferiority analysis.

The efficacy results are presented in Table 6. Figures 5 and 6 show Kaplan-Meier plot of these data for Trials 9238IL/0020 and 9238IL/0021, respectively.

Table 6 Trials 9238IL/0020 and 9238IL/0021 - Efficacy Results

End Point	North American Trial (9238IL/0021)		Predominantly European Trial (9238IL/0020)		Combined Trials (9238IL/0021 & 9238IL/0020)	
	FASLODEX 250 mg (n=206)	Anastrozole 1 mg (n=194)	FASLODEX 250 mg (n=222)	Anastrozole 1 mg (n=229)	FASLODEX 250 mg (n=423)	Anastrozole 1 mg (n=423)
Time to Progression (TTP) Median TTP (days)	167.4	103.5	167.4	155.2	167.6	124.8
Hazard Ratio (FAS/ANA) 2-sided 95.14%	0.92 (0.74, 1.14)		0.98 (0.80, 1.21)		0.95 (0.82, 1.10)	
Objective Tumour Response Number (%) of subjects with CR + PR	36 (17.5)	34 (17.5)	46 (20.7)	36 (15.7)	82 (19.2)	70 (16.5)
% Difference in Tumour Response Rate (FAS/ANA) 2-sided 95.14% CI	+0.2% (-6.3, +9.3)		+4.8% (-2.2, +14.2)		+2.8% (-2.3, +9.0)	
Survival Time Died n (%) Median Survival (days)	152 (73.8%) 844	149 (76.8%) 913	167 (75.2%) 803	173 (75.5%) 736	319 (74.5%) 833	322 (76.1%) 844
Hazard Ratio 2-sided 95% CI	0.98 (0.78, 1.24)		0.97 (0.78, 1.21)		0.98 (0.84, 1.15)	

CR = Complete Response; PR = Partial Response; CI = Confidence Interval

FAS = FASLODEX

ANA = Anastrozole

Figure 5 Kaplan Meier Probability of Time to Progression (patients included: all patients randomised to fulvestrant 250 mg or anastrozole 1 mg - predominantly European Trial; 9238IL/0020)

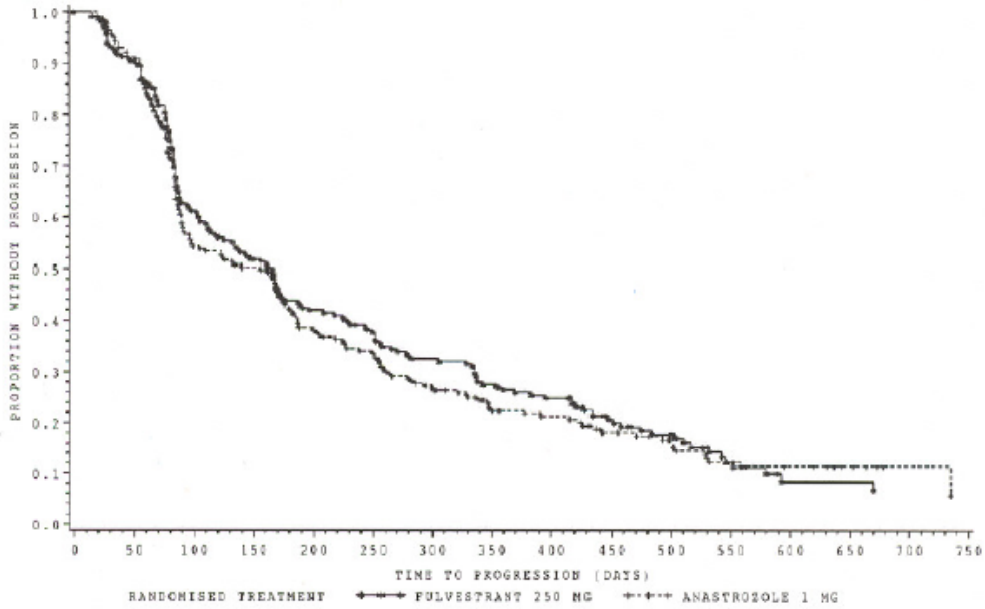
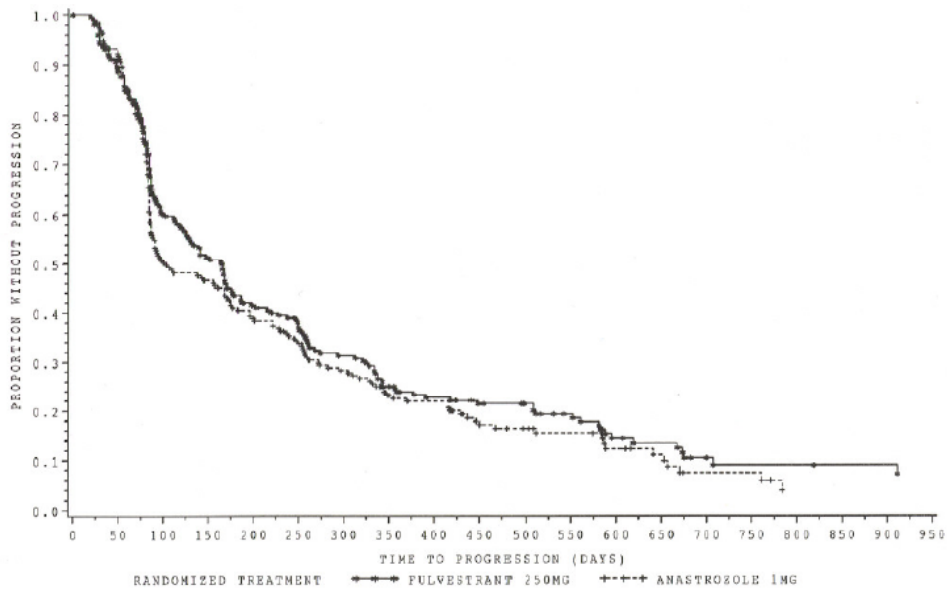


Figure 6 Kaplan Meier Probability of Time to Progression (patients included: all patients randomised to fulvestrant 250 mg or anastrozole 1 mg - North American Trial; 9238IL/0021)



Comparison of FASLODEX 500 mg and FASLODEX 250 mg

A Phase III clinical trial (CONFIRM; Trial D6997C00002) 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). Time to progression (TTP), defined as the time from randomisation to the time of the earliest evidence of objective disease progression or death from any cause was the primary endpoint. Objective response rate (ORR), overall survival (OS), clinical benefit rate (CBR), duration of response (DoR), and duration of clinical benefit (DoCB), were all secondary efficacy endpoints.

FASLODEX 500 mg was administered as two 5 mL injections each containing FASLODEX 250 mg/5 mL, once in each buttock on Days 0, 14, 28 and every 28 (+/- 3) days thereafter. FASLODEX 250 mg was administered as two 5 mL injections (one containing FASLODEX 250 mg/5 mL injection plus one placebo injection) one in each buttock on Days 0, 14 (2 placebo injections only), 28 and every 28 (+/-) days thereafter

Table 7 provides the demographics and baseline characteristics of the postmenopausal women randomized to FASLODEX 500 mg or FASLODEX 250 mg.

Table 7 CONFIRM (Trial D6997C00002) - Demographics and baseline characteristics

Parameter	Trial D6997C00002	
	FASLODEX 500 mg	FASLODEX 250 mg
No. of Participants	362	374
Median Age (yrs)	61.0	61.0
Age Range (yrs)	26–91	23–87
Hormone Receptor Status # (%)		
ER+ve	362 (100.0)	374 (100.0)
PgR+ve	241 (66.6)	266 (71.1)
PgR-ve	92 (25.4)	96 (25.7)
PgR unknown	29 (8.0)	12 (3.2)
Disease Characteristics (at randomization)		
Locally advanced breast cancer only	4 (1.1)	11 (2.9)
Metastatic disease	358 (98.9)	363 (97.1)
Any visceral disease	205 (56.6)	198 (52.9)

Bone only	87 (24.0)	77 (20.6)
Measurable Disease		
No	112 (30.9)	113 (30.2)
Yes	240 (66.3)	261 (69.8)
Previous Therapy		
Adjuvant therapy ^a		
Endocrine therapy	231 (63.8)	249 (66.6)
Aromatase inhibitor	52 (14.4)	55 (14.7)
Anti-estrogen	202 (55.8)	217 (58.0)
Chemotherapy	185 (51.1)	200 (53.5)
Radiotherapy	214 (59.1)	206 (55.1)
Advanced disease therapy ^a		
Endocrine therapy	173 (47.8)	182 (48.7)
Aromatase inhibitor	101 (27.9)	108 (28.9)
Antiestrogen	72 (19.9)	75 (20.1)
Chemotherapy	81 (22.4)	69 (18.4)
Radiotherapy	69 (19.1)	102 (27.3)
Last endocrine therapy received ^b		
Aromatase inhibitor	52 (42.0)	161 (43.0)
Antiestrogen	210 (58.0)	213 (57.0)

^a Categories are not mutually exclusive.

^b Patients who had received 2 previous endocrine therapies could be eligible provided that they have started the advanced endocrine treatment at least 12 months after the completion of adjuvant endocrine treatment.

Trial results

Time to Progression (TTP) for FASLODEX 500 mg was significantly longer than for FASLODEX 250 mg (Hazard ratio [95% CI] = 0.80 [0.68 to 0.94]; p=0.006).

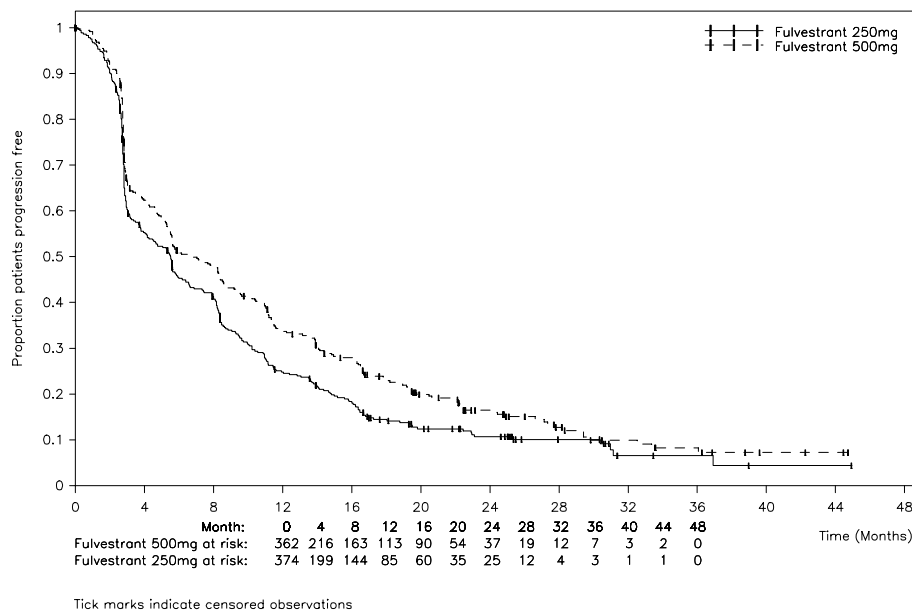
Table 8 shows the TTP data for all randomised patients to the FASLODEX 500 mg or FASLODEX 250 mg treatment arms in CONFIRM (Trial D6997C00002); Figure 7 shows a Kaplan-Meier plot of these data.

Table 8 CONFIRM (Trial D6997C00002) - Summary of time to progression (TTP): Includes all randomised patients to either FASLODEX 500 mg or FASLODEX 250 mg

	FASLODEX 500 mg N=362	FASLODEX 250 mg N=374
Number progressed (%)	297 (82.0)	321 (85.8)
Median (months)	6.5	5.5
Time to progression (months): 25% quartile	2.8	2.7
Time to progression (months): 75% quartile	16.6	11.9
Percentage of patients progression free at:		
6 months	51%	45%
12 months	34%	25%
18 months	23%	14%
24 months	16%	11%
Hazard ratio (95% CI)	0.80 (0.68–0.94)	
p-value	0.006	

Time to progression is the time between randomisation and the earliest of progression or death from any cause. A hazard ratio <1 indicates FASLODEX 500 mg is associated with a longer time to disease progression than FASLODEX 250 mg. A hazard ratio >1 indicates FASLODEX 500 mg is associated with a shorter time to disease progression than FASLODEX 250 mg.

Figure 7 CONFIRM (Trial D6997C00002) - Kaplan-Meier plot of time to progression: Includes all patients randomised to either FASLODEX 500 mg or FASLODEX 250 mg in CONFIRM trial



The primary analysis of TTP is supported by the Cox proportional hazards regression analysis, adjusted for treatment and 6 specified covariates (hazard ratio=0.78 [95% CI 0.67 to 0.92]; p=0.003).

Subgroup analyses of the primary endpoint (TTP) were performed for 6 pre-defined covariates: receptor status, visceral involvement, response to last endocrine therapy, measurable disease, age and last endocrine therapy received prior to fulvestrant. The observed treatment effect in favour of fulvestrant 500 mg over fulvestrant 250 mg was consistent across all subgroups. A global interaction test on TTP was conducted to determine whether there was any heterogeneity in the treatment effect across the 6 predefined covariates; no evidence of heterogeneity was found (p=0.801). Nevertheless, it is important to mention that the study was not powered to detect interaction between the investigated covariates and treatment activity.

Table 9 shows the efficacy results for the secondary outcome variables.

Table 9 CONFIRM (Trial D6997C00002) Summary of efficacy results for the secondary endpoints

Variable	fulvestrant 500mg	fulvestrant 250mg	
Objective response rate	13.8%	14.6%	Odds ratio=0.94 (95% CI 0.57–1.55); p=0.795
Clinical benefit rate	45.6%	39.6%	Odds ratio=1.28 (95% CI 0.95–1.71); p=0.100
Duration of response ^a (median)	19.4 months	16.4 months	Ratio of expected duration of response=0.894 (95% CI 0.479–1.667); p=0.724
Duration of clinical benefit (median)	16.6 months	13.9 months	Ratio of expected duration of clinical benefit=1.357 (95% CI 1.067–1.726); p=0.013
Overall survival (median)	25.1 months	22.8 months	Hazard ratio=0.84 (95% CI 0.69–1.03); p=0.091

^a measured from randomisation to progression

A hazard ratio <1 indicates fulvestrant 500 mg is associated with a longer time to disease progression than fulvestrant 250 mg
 A hazard ratio >1 indicates fulvestrant 500 mg is associated with a shorter time to disease progression than fulvestrant 250 mg
 An odds ratio >1 favours fulvestrant 500 mg whereas an odds ratio of <1 favours fulvestrant 250mg

Effects on breast cancer tissue *in vivo*

Clinical trials in postmenopausal women with primary breast cancer have shown that fulvestrant significantly downregulates estrogen receptor (ER) expression in ER positive tumours in a dose dependent manner. There was also a significant decrease in progesterone receptor (PR) expression, an estrogen-regulated protein consistent with the preclinical data demonstrating that fulvestrant lacks intrinsic estrogen agonist activity. These changes in ER and PR expression were accompanied by reductions in expression of Ki67, a marker of tumour cell proliferation, which were also related to dose with fulvestrant 500 mg having a significantly greater effect than the 250 mg dose.

Effects on the postmenopausal endometrium

Data suggests that FASLODEX will not have a stimulatory effect on the postmenopausal endometrium. A trial in healthy postmenopausal volunteers showed that compared to placebo, pre-treatment with 250 mg FASLODEX resulted in significantly reduced stimulation of the postmenopausal endometrium in volunteers treated with 20 mcg per day ethinyl oestradiol. This demonstrates an antiestrogenic effect on the postmenopausal endometrium.

Treatment for up to 16 weeks in breast cancer patients treated with either FASLODEX 500 mg or 250 mg did not result in clinically significant changes in endometrial thickness, indicating of a lack of agonist effect.

Effects on bone

Treatment for up to 16 weeks in breast cancer patients treated with either FASLODEX 500 mg or 250 mg did not result in clinically significant changes in serum bone-turnover markers. There are no long-term data on the effect of fulvestrant on bone. Due to the mode of action of fulvestrant, there is a potential risk of osteoporosis.

DETAILED PHARMACOLOGY

Pharmacodynamics

Fulvestrant is a potent inhibitor of the growth of ER positive MCF-7 human breast cancer cells.

In intact adult female rats, treatment with fulvestrant proved effective in blocking the trophic action of endogenous estrogens on the uterus. The potency of fulvestrant against endogenous estrogen ($ED_{50} \approx 0.1$ mg/kg/day subcutaneous) was similar to that found in the ovariectomized, estradiol-treated rat ($ED_{50} \approx 0.07$ mg/kg subcutaneous).

Changes in the cornification of the vaginal smears also indicated a similar potency of fulvestrant against estrogen effects on the vagina (partial and complete blockade at 0.1 and 0.3 mg/kg subcutaneous, respectively).

The anti-tumour activity of fulvestrant was assessed in mice bearing tumours derived from the MCF-7 human breast cancer cell line or from explants of the human breast tumour-derived solid tumour, Br10. A single subcutaneous injection of 5 mg of fulvestrant blocked completely the growth of MCF-7-derived human breast tumour xenografts in nude mice for at least four weeks. The growth of transplants of the Br10 human breast tumour was also suppressed effectively by fulvestrant. A single subcutaneous injection of 5 mg fulvestrant on the day of tumour implantation showed a substantial and sustained reduction of tumour growth, compared with controls. Ovariectomy of all the animals after 3 months demonstrated the estrogen sensitivity of the tumours.

Independent studies showed that tamoxifen-resistant MCF-7 xenografts in nude mice, which grow out after long-term treatment with tamoxifen, remain sensitive to fulvestrant treatment.

Pharmacokinetics

Fulvestrant was well absorbed and widely distributed into the tissues following intramuscular administration, and is eliminated almost entirely in bile in rats and dogs. Metabolism was qualitatively similar in rats, dogs and man. Although some metabolites possess intrinsic activity similar to the parent, they were not detectable in the plasma and were quantitatively minor metabolites (<10%). The results suggest that fulvestrant itself is responsible for the observed pharmacological activity *in vivo*. Adequate exposure to fulvestrant was achieved in the rat and dog relative to man.

In rats, fulvestrant was generally released slowly from the long-acting formulation throughout a 30-day measurement period. T_{max} was variable (between 3 hours and 11 days after dosing) and group mean AUC (0-30 days) increased proportional to dose. In dogs, group mean AUC(0-28 days) was also dose proportional and the time to C_{max} (T_{max}) varied between 2 and 7 days. Monthly intramuscular injections to dogs resulted in a slight accumulation, but there was no evidence of an increase in C_{max} .

TOXICOLOGY

Acute Toxicity

The acute toxicity of FASLODEX (fulvestrant) is low. In rodents, the median lethal dose was greater than 70 mg/kg following intramuscular administration (more than 400-times the clinical dose), greater than 50 mg/kg following intravenous administration, and greater than 2000 mg/kg following oral administration.

Repeat Dose Toxicity

FASLODEX was well tolerated in all animal species in which it was tested. In multiple, intramuscular dose toxicity studies in rats and dogs, the antiestrogenic activity of FASLODEX was responsible for most of the effects seen, particularly in the female reproductive system, but also in other organs sensitive to hormones in both sexes. There was no evidence of other systemic toxicity in rats dosed up to 10 mg/rat/15 days for 6 months or in dogs dosed up to 40 mg/kg/28 days for 12 months.

In dog studies following oral and intravenous administration, effects on the cardiovascular system (slight elevations of the S-T segment of the ECG [oral], and sinus arrest in one dog [intravenous]) were seen, but these occurred in animals exposed to far higher levels of FASLODEX than those recorded in patients (C_{max} >15 times) and are, therefore, considered to be of no significance for human safety at the clinical dose.

Carcinogenicity and Mutagenicity

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 0.9-, 1.5-, and 3-fold (in females) and 0.8-, 0.8-, and 2.0-fold (in males) the systemic exposure [$AUC_{0-30\text{ days}}$] achieved in women receiving the recommended dose of 500 mg/month. An increased incidence of benign ovarian granulosa cell tumours and testicular Leydig cell tumours was evident, in females dosed at 10 mg/rat/15 days and males

dosed at 15 mg/rat/30 days, respectively. In a two-year mouse oncogenicity study, oral dosing was associated with an increased incidence of sex cord stromal tumours (both benign and malignant) in the ovary at doses of 150 and 500 mg/kg/day. The no-observed-effect level (NOEL) for these findings was 10 mg/rat/30 days in the rats and 20 mg/kg/day in the mice, respectively. Induction of such tumours is consistent with the pharmacology-related endocrine feedback alterations in gonadotropin levels caused by an antiestrogen. Therefore these findings are not considered to be relevant to use of fulvestrant in postmenopausal women.

Fulvestrant was not mutagenetic 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).

Reproduction and Teratology

In a variety of reproductive toxicology studies, rats were dosed intramuscularly with 0.001 - 2 mg/kg/day (0.007 - 13 mg/m², based on body surface area) and rabbits were dosed with 0.01 - 0.25 mg/kg/day (0.1 - 2.5 mg/m², based on body surface area). In comparison, the human clinical dose, 500 mg/month, equates to approximately 13.4 mg/m². On a mg/m² basis, these animal studies showed that at doses similar to, or lower than the clinical dose of FASLODEX, there were effects upon reproduction as well as embryo/fetal development consistent with its antiestrogenic activity. FASLODEX has been shown to cross the placenta following single intramuscular doses of 1.0 mg/kg in rats and 0.26 mg/kg in rabbits.

In rats, FASLODEX caused a reversible reduction in female fertility and in embryonic survival at dose levels of 0.01 mg/kg/day and above (approximately 0.6% of the human dose, based on body surface area), dystocia, and an increased incidence of fetal abnormalities, including tarsal flexure. Dosing with 0.1 mg/kg/day and above (approximately 6% of the human dose on a body surface area basis) resulted in evidence of delayed fetal development including an increased incidence in non-ossification of the odontoid and the ventral tubercle of the first cervical vertebra. An increased incidence in tarsal flexure was seen with 2.0 mg/kg/day (equivalent to the human dose on a mg/m² basis) when FASLODEX was administered during organogenesis. Other major fetal anomalies occurring at 2 mg/kg/day included the following: edema, gastroschisis, shortened digits, flexion of the hindpaw, and shortening of the upper and lower jaw.

Rabbits given FASLODEX (\geq 1mg/kg/day, equivalent to the human dose on a mg/m² basis), during the period of major organogenesis, failed to maintain pregnancy. In addition, at 0.25 mg/kg/day (one-quarter the human dose on a mg/m² basis), increases in placental weight and post-implantation loss were seen, but no fetal abnormalities were observed. There was, however, an increased incidence of fetal variations, common in rabbits (backwards displacement of the pelvic girdle, and 27 pre-sacral vertebrae) at 0.25 mg/kg/day (one-quarter the human dose on a mg/m² basis), when dosed during the period of organogenesis.

The potential effects of FASLODEX on the fertility of male animals were not studied, however, 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, FASLODEX 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 FASLODEX doses correspond to approximately 1.3-, 1.2-, and 3.5-fold the systemic exposure [$AUC_{0-30 \text{ days}}$] achieved in women receiving the recommended dose of 500mg/month.

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PART III: CONSUMER INFORMATION

Pr FASLODEX®
fulvestrant injection
50 mg/mL

This leaflet is part III of a three-part "Product Monograph" published when FASLODEX was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about FASLODEX. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

FASLODEX is used to treat breast cancer in postmenopausal women.

What it does:

In hormone sensitive breast cancer, estrogen (female sex hormone) promotes tumour growth. By stopping some of the actions of estrogen, FASLODEX reduces the amount that is in the body, which has an effect in reducing breast cancer tumour growth.

When it should not be used:

- If you are allergic to this drug or any of its ingredients (see important nonmedicinal ingredients).
- If you are pregnant or breast-feeding.

What the medicinal ingredient is:

fulvestrant

What the important nonmedicinal ingredients are:

ethanol, benzyl alcohol, benzyl benzoate and castor oil.

What dosage forms it comes in:

Sterile injection solution in pre-filled syringes. Each pre-filled syringe has 250 mg of fulvestrant.

WARNINGS AND PRECAUTIONS

FASLODEX is not expected to affect your ability to drive or use machines. However, some patients may occasionally feel tired and/or weak. If this happens to you, do not drive or operate machines and ask your doctor for advice. FASLODEX should not be given to children or men.

BEFORE you use FASLODEX talk to your doctor or pharmacist if:

- If you have any problems with your liver or kidneys;
- If you have been told you have a low blood platelet count, problems with bleeding or if you use medicine to prevent blood clots (e.g. anticoagulants).
- If you have a personal or family history of osteoporosis (thinning of the bone), or have low bone density, or have a recent history of fracture.

INTERACTIONS WITH THIS MEDICATION

Interactions with other drugs and FASLODEX have not been established. Before using FASLODEX talk to your doctor or pharmacist if you are taking, or have recently taken any other medicines, even those you have bought without prescription.

PROPER USE OF THIS MEDICATION

FASLODEX is to be given as an injection into the muscle (intramuscular) of the buttock.

Usual dose:

500 mg once a day as two 250 mg/5 mL injections, one in each buttock on days 0, 14 and 28 and then every 28 days thereafter.

Overdose:

In case of suspected drug overdose, contact a health care practitioner, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss your scheduled dose, call your doctor immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, FASLODEX can have side effects. Tell your doctor as soon as possible if any of the following side effects bothers you or continues.

SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Very Common (more than 10 of every 100 patients have these events)			
injection site reactions, such as pain and/or inflammation		√	
weakness		√	
nausea		√	
changes in the level of liver enzymes (when a blood test is taken)		√	
Common (1 to 10 of every 100 patients have these events)			
hot flushes		√	
headache		√	
symptoms from the stomach or the bowels, such as vomiting, diarrhea or loss of appetite		√	
skin rash		√	
bladder infections		√	
Contact your doctor promptly if the following happens to you, as you may need further examination or treatment			
Allergic reactions, including swelling of the face, lips, tongue and/or throat, hives/welts and/or difficulty with swallowing. Such reactions may happen immediately, or several days after injection.		√	

If you notice any other side effects, please tell your doctor or pharmacist as soon as possible.
This is not a complete list of side effects. For any unexpected effects while taking FASLODEX, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach and sight of children.

FASLODEX must be kept in the refrigerator (2°C-8°C). The pre-filled syringe will normally be stored for you by your doctor or the hospital. The staff is responsible for the correct storage, use and disposal of FASLODEX.

Keep the FASLODEX syringe in its original pack and do not break the seal, in order to protect it from light. The FASLODEX pre-filled syringe should not be used after the expiry date on the pack.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice

MORE INFORMATION

NOTE: This Consumer Information Leaflet provides you with the most current information at the time of printing.

For the most current information, the Consumer Information Leaflet plus the full Product Monograph, prepared for health professionals can be found at: www.astrazeneca.ca, under Patients with Prescriptions or by contacting the sponsor, AstraZeneca Canada Inc. at:
 Customer Inquiries – 1 (800) 668-6000,
 Renseignements – 1 (800) 461-3787.

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