FASLODEX ™

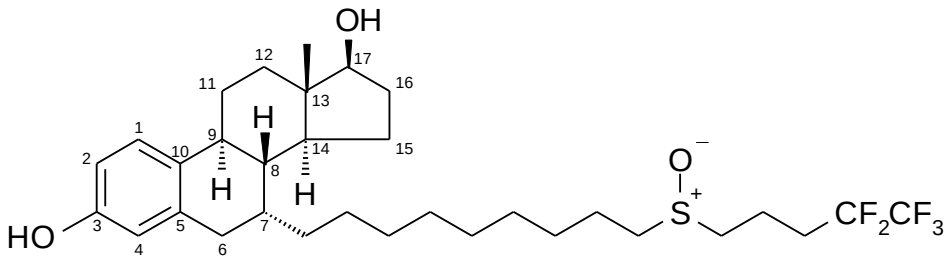
fulvestrant

PRODUCT INFORMATION

NAME OF THE MEDICINE

The active ingredient in FASLODEX is fulvestrant. The chemical name is 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]estra-1,3,5(10)-triene-3,17β-diol.

The chemical structure of fulvestrant is



CAS number 129453-61-8

Molecular formula $C_{32}H_{47}F_5O_3S$

MW 606.8

DESCRIPTION

Fulvestrant is a white powder with low aqueous solubility. Only 1 morphological form is known to exist. Fulvestrant is highly lipophilic and does not ionise at physiological pH.

FASLODEX 250 mg/5 mL solution for injection is a clear, colourless to yellow, viscous liquid.

In addition to fulvestrant, FASLODEX also contains ethanol 96%, benzyl alcohol, benzyl benzoate and castor oil.

PHARMACOLOGY

Pharmacodynamics

Fulvestrant is an antioestrogen that binds to oestrogen receptors in a competitive manner, with a high affinity comparable to that of oestradiol, and downregulates the oestrogen receptor. Fulvestrant completely inhibited the uterotrophic action of exogenous oestradiol, but showed no agonistic effects in uterotrophic assays in immature or ovariectomised mice, rats and monkeys. Thus it appears to have antioestrogen activity without having any partial agonist (oestrogen-like) activity.

Fulvestrant inhibited the growth of the oestrogen-sensitive human breast cancer cell line MCF-7 *in vitro* and of xenografts of MCF-7 cells in nude mice. Fulvestrant inhibited the growth of tamoxifen-resistant breast cancer cells *in vitro* and of tamoxifen-resistant breast tumours in nude mice.

Effects on breast cancer tissue in vivo:

Clinical trials in postmenopausal women with primary breast cancer have shown that fulvestrant significantly downregulates oestrogen receptor expression in oestrogen receptor positive tumours compared with placebo and tamoxifen. There was also a significant decrease in progesterone receptor expression consistent with the preclinical data demonstrating that fulvestrant lacks intrinsic oestrogen agonist activity. These changes in oestrogen receptor and progesterone receptor 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:

The preclinical data for fulvestrant suggest that it 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 fulvestrant resulted in significantly reduced stimulation of the postmenopausal endometrium in volunteers treated with 20 micrograms per day ethinyl oestradiol. This demonstrates a potent antioestrogenic effect on the postmenopausal endometrium.

Pharmacokinetics

After administration of FASLODEX long-acting intramuscular injection, fulvestrant is slowly absorbed and maximum plasma concentrations are reached after about 7 days. Absorption continues for over one month and monthly administration results in an approximate 2-fold accumulation. Steady-state levels are reached after about 6 doses during monthly injections with the major part of the accumulation achieved after 3-4 doses. The terminal half-life is governed by the absorption rate and was estimated to be 50 days. At steady state, fulvestrant plasma concentrations are maintained within a relatively narrow range with approximately 2- to 3-fold difference between maximum and trough concentrations.

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

Administration of FASLODEX 500 mg at day 0 and 14 achieves exposure levels at or close to steady state within the first month of dosing (mean [CV]): AUC 475 (33.4%) ng.days/mL, C_{max} 25.1 (35.3%) ng/mL, C_{min} 16.3 (25.9%) ng/mL, respectively).

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. Very low density lipoprotein (VLDL), low density lipoprotein (LDL), and high density lipoprotein (HDL) fractions are the major binding components. Therefore no drug interaction studies were conducted on competitive protein binding. The role of sex hormone-binding globulin has not been determined.

Metabolism

The metabolism of fulvestrant has not been fully evaluated, but involves combinations of a number of possible biotransformation pathways analogous to those of endogenous steroids (includes 17-ketone, sulphone, 3-sulphate, 3- and 17-glucuronide metabolites). Identified metabolites are either less active or exhibit similar activity to fulvestrant in anti-oestrogen models. Studies using human liver preparations and recombinant human enzymes indicate that CYP 3A4 is the only P450 isoenzyme involved in the oxidation of fulvestrant, however non-P450 routes appear to be more predominant *in vivo*.

Elimination

Fulvestrant is eliminated mainly by metabolism. The major route of excretion is via the faeces with less than 1% being excreted in the urine. Fulvestrant has a high clearance, 11±1.7 mL/min/kg, suggesting a high hepatic extraction ratio.

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.(see PRECAUTIONS)

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 patients 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 and DOSAGE & ADMINISTRATION sections).

Other populations

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

No difference in fulvestrant pharmacokinetic profile was detected with regard to ethnic groups.

CLINICAL TRIALS

Effects on advanced breast cancer

A Phase III clinical trial (CONFIRM) 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). Progression free survival (PFS) was the primary endpoint; key secondary efficacy endpoints included objective response rate (ORR); clinical benefit rate (CBR) and overall survival (OS). PFS for FASLODEX 500 mg was significantly longer than for FASLODEX 250 mg. Efficacy results are summarized in Table 1 and Figure 1 below. In the initial Overall Survival (OS) analysis after a minimum follow-up duration of 18 months, there was no statistically significant difference in OS between the two treatment groups. After a minimum follow-up duration of 50 months, an updated OS analysis was performed. Final OS analysis at 75% maturity showed that Faslodex 500 mg was associated with a 4.1-month increase in median OS and a 19% reduction in the risk of death compared with Faslodex 250 mg [HR=0.81; 95% CI 0.69-0.96; p = 0.016 (nominal p-value as no adjustment was made for multiplicity)].

Table 1 Efficacy results for the CONFIRM study: Intention To Treat Population

Endpoint	**Fulvestrant 500 mg (N = 362)**	**Fulvestrant 250 mg (N = 374)**
PFS[a] Median (months)	6.5	5.4
Hazard Ratio[b] (95% CI[c])	0.80 (0.68 – 0.94)	
p-value	0.006	
OS[d] Updated Analysis (% of patients who died)	**261 (72.1%)**	**293 (78.3%)**
Median OS (months)	26.4	22.3
Hazard Ratio[b] (95% CI[c])[f]	0.81 (0.69 – 0.96)	
ORR[g] (95% CI[c])	13.8% (9.7%, 18.8%) (33/240)	14.6% (10.5%, 19.4%) (38/261)

[a] PFS (Progression Free Survival) = the time between randomisation and the earliest of progression or death from any cause. Minimum follow-up duration of 18 months.

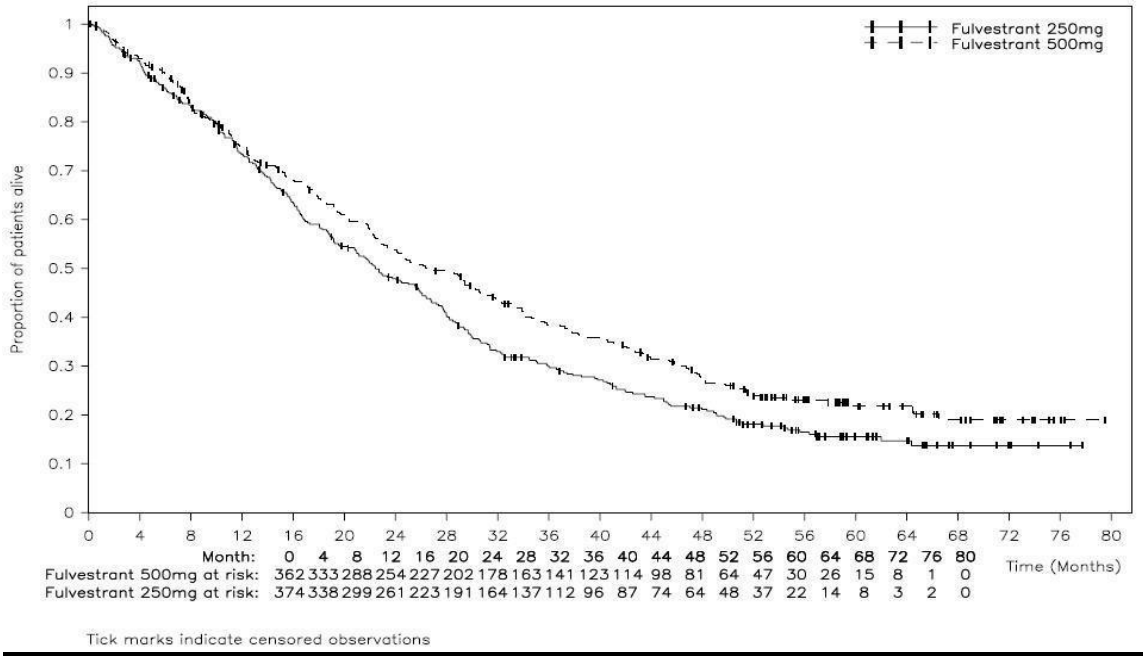
[b] Hazard ratio <1 favours FASLODEX 500 mg.

[c] CI = Confidence Interval [d] OS = Overall Survival [e] Minimum follow-up duration of 50 months.

[f] Not statistically significant as no adjustments were made for multiplicity.

[g] ORR (Objective Response Rate), defined as the number (%) of patients with complete or partial response, was analysed in the evaluable patients with measurable disease at baseline (fulvestrant 500 mg N = 240; fulvestrant 250 mg N = 261). Minimum follow-up duration of 18 months.

Figure 1 Kaplan-Meier plot of the updated Overall Survival data for the CONFIRM study



Irrespective of the last endocrine therapy (anti-oestrogen or aromatase inhibitor), the treatment effect (PFS) for FASLODEX 500 mg vs. FASLODEX 250 mg was consistent. There was no significant difference in clinical benefit rate for patients receiving FASLODEX 500 mg vs 250 mg (45.6% vs 39.6%; odds ratio 1.28 [95% CI 0.95, 1.71]; p=0.1) or in duration of clinical benefit (median 16.6 vs 13.9 months for FASLODEX 500 mg and FASLODEX 250 mg, respectively).

Two Phase III clinical trials (Study 9238IL/0020 & 9238IL/0021) were completed in a total of 851 postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. These trials compared the safety and efficacy of FASLODEX with a third-generation aromatase inhibitor, anastrozole. Both trials used a dose of 250 mg every 28 days. The primary endpoint was progression free survival.

Overall, FASLODEX 250 mg was at least as effective as anastrozole in terms of progression free survival (PFS), objective response, clinical benefit, time to treatment failure and quality of life.

In Study 21, median PFS was 165 days with fulvestrant and 103 days with anastrozole (HR 0.92; 95% CI: 0.74 - 1.14). In Study 20, median PFS was 166 days with fulvestrant and 156 days with anastrozole (HR 0.98; 95% CI: 0.80 - 1.21)

FASLODEX 250 mg had an objective response rate of 20.7% in Study 20 (vs 15.7% with anastrozole) and 17.5% in Study 21 (vs 17.5% with anastrozole).

FASLODEX 250 mg showed durable responses in both trials. In Study 20, the median duration of response was 19.3 months for FASLODEX 250 mg and 10.5

months for anastrozole. In Study 21, the median duration of response was 14.3 months and 14.0 months for FASLODEX 250 mg and anastrozole 1 mg respectively.

The majority of patients in these trials had ER+ and/or PgR+ tumors (about 80%). Patients who had ER-/PgR- or unknown disease must have shown prior response to endocrine therapy.

There are no efficacy data to support use of FASLODEX in premenopausal patients with advanced breast cancer.

INDICATIONS

FASLODEX is indicated for the treatment of postmenopausal women with hormone-receptor positive, locally advanced or metastatic breast cancer who have progressive disease following prior tamoxifen therapy.

CONTRAINDICATIONS

FASLODEX is contraindicated in patients with a known hypersensitivity to the drug substance or to any of the excipients.

FASLODEX is contraindicated in pregnancy.

PRECAUTIONS

Hepatic impairment

Fulvestrant is metabolised primarily in the liver. In clinical trials in patients with advanced breast cancer, in which FASLODEX has been administered to patients with mild hepatic impairment (alanine aminotransferase concentration greater than the upper limit of the normal reference range [ULN] but less than twice the ULN) there was no clear relationship between fulvestrant clearance and hepatic impairment. The safety profile in patients with mild hepatic impairment was similar to that seen in patients with no hepatic impairment. Caution should be used with FASLODEX in patients with moderate to severe hepatic impairment, as clearance may be reduced.

Renal impairment

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

Coagulation disorders

Caution should be used before treating patients with bleeding diatheses or thrombocytopenia or patients on anticoagulants due to the route of administration.

Effects on fertility

Fulvestrant affected oestrus cycling in rats causing a reduction in female fertility at doses as low as 0.01 mg/kg/day, considerably lower than the clinical dose on a body surface area basis. Embryonic survival was also reduced. These effects are consistent with the antioestrogenic activity of fulvestrant. These effects were largely reversible in rats after a 1-month withdrawal period from the drug. FASLODEX is not proposed for use in males, but loss of spermatozoa from the seminiferous tubules, seminiferous tubular atrophy and degenerative changes in the epidiymides were observed in a 6-month study in rats given fulvestrant by the intramuscular route.

Use in pregnancy (Category D)

FASLODEX is proposed for use in postmenopausal women only. FASLODEX may cause foetal harm when administered to a pregnant woman. If FASLODEX is used during pregnancy or if the patient becomes pregnant while receiving this drug, the patient should be informed of the potential hazard to the foetus or potential risk for loss of the pregnancy. In rats, fulvestrant caused a reversible reduction in embryonic survival at intramuscular doses as low as 0.01 mg/kg/day, considerably lower than the clinical dose calculated on a body surface area basis. Fulvestrant also caused dystocia and an increased occurrence of foetal abnormalities in rats, including tarsal flexure, at an intramuscular dose of 2 mg/kg/day, corresponding to approximately twice the clinical dose calculated on a body surface area basis. Rabbits given intramuscular fulvestrant at ≥1 mg/kg/day (corresponding to approximately twice the clinical dose calculated on a body surface area) failed to maintain pregnancy, while at doses of 0.25 mg/kg/day, there were small increases in post-implantation loss, placental weight and incidences of two foetal variations.

Use during lactation

Studies in rats have shown that fulvestrant levels in rat milk are significantly higher than those in rat plasma. The potential risk for nursing infants is unknown. Therefore breastfeeding should be avoided in women receiving FASLODEX.

Paediatric use

Not recommended for use in children or adolescents as safety and effectiveness have not been established in this age group.

Genotoxicity

FASLODEX showed no genotoxic potential in bacterial reverse mutation assays, *in vitro* mouse lymphoma assays, an *in vitro* chromosome aberration assay in human lymphocytes, and an *in vivo* micronucleus assay in rats.

Carcinogenicity

A two-year rat oncogenicity study (intramuscular administration with the FASLODEX formulation) showed increased incidence of benign ovarian granulosa cell tumours in females at the high dose, 10 mg/rat/15 days (approx 5-times the human dose based on plasma AUC values). Induction of such tumours is consistent with the pharmacology-related endocrine feedback alteration in gonadotropin levels caused by anti-oestrogen in cycling animals. Therefore this

finding is not considered to be clinically relevant to the use of fulvestrant in postmenopausal women with advanced breast cancer.

Injection site related events

Injection site related events including sciatica, neuralgia, neuropathic pain, and peripheral neuropathy have been reported with FASLODEX injection. Caution should be taken while administering FASLODEX at the dorsogluteal injection site due to the proximity of the underlying sciatic nerve (see DOSAGE AND ADMINSTRATION and ADVERSE EFFECTS).

Effects on ability to drive and operate machinery

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.

INTERACTIONS WITH OTHER DRUGS

Fulvestrant does not significantly inhibit any of the major cytochrome P450 (CYP) isoenzymes in vitro, and results from a clinical pharmacokinetic trial involving co-administration of fulvestrant with midazolam 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 with rifampicin showed no change in fulvestrant clearance as a result of the induction of CYP3A4. Dosage adjustment is not necessary in patients co-prescribed CYP3A4 inhibitors or inducers.

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

Interference with oestradiol assay

Due to the structural similarity of fulvestrant and oestradiol, fulvestrant may interfere with antibody based oestradiol assays and may result in falsely increased levels of oestradiol.

ADVERSE EFFECTS

The following frequency categories for adverse drug reactions (ADRs) were calculated based on the FASLODEX 500 mg treatment group in pooled safety analyses of studies that compared FASLODEX 500 mg with FASLODEX 250 mg [CONFIRM (Study D6997C00002), FINDER 1 (Study D6997C00004), FINDER 2 (Study D6997C00006), and NEWEST (Study D6997C00003) studies], or from FALCON (Study D699BC00001) that compared FASLODEX 500 mg with anastrozole 1 mg. Where frequencies differ between the pooled safety analysis and FALCON, the highest frequency is presented. The frequencies in the following table were based on all reported events, regardless of the investigator assessment of causality.

Table 2 Summary of Adverse Drug Reactions (ADR) seen in clinical trials for FASLODEX 500 mg

Frequency descriptor	System Order Class	ADR
Very common (≥ 10%)	General disorders and administration site conditions	Injection site reactions[c], asthenia
	Hepatobiliary disorders	Elevated liver enzymes (ALT, AST, ALP)[a]
	Gastrointestinal disorders	Nausea
	Immune system disorders	Hypersensitivity reactions[e]
	Musculoskeletal and connective tissue disorders	Joint and musculoskeletal pain[d]
	Skin and subcutaneous tissue disorders	Rash[e]
	Vascular disorders	Hot flushes[e]
Common (≥1 - <10%)	Nervous system disorders	Headache
	Hepatobiliary disorders	Elevated bilirubin[a]
	Blood and lymphatic system	Reduced platelet count[e]
	Gastrointestinal disorders	Vomiting, diarrhoea
	Metabolism and nutrition disorders	Anorexia
	Infections and infestations	Urinary tract infections
Uncommon (≥0.1% and <1%)	Hepatobiliary disorders	Hepatic failure[b,f], hepatitis[f], elevated gamma-GT[f]

[a] Based on any CTC grade change from baseline.

[b] The event was not observed in major clinical studies (CONFIRM, FINDER1, FINDER2, NEWEST). The frequency has been calculated using the upper limit of the 95% confidence interval for the point estimate. This is calculated as 3/560 (where 560 is the number of patients in the major clinical studies), which equates to a frequency category of 'uncommon'

[c] Including more severe injection site related sciatica, neuralgia, neuropathic pain, and peripheral neuropathy.

[d] Includes: arthralgia, and less frequently musculoskeletal pain, back pain, myalgia and pain in extremity.

[e] Frequency category differs between pooled safety dataset and FALCON.

[f] ADR was not observed in FALCON.

In the combined studies (CONFIRM, NEWEST, FIRST, FINDER1 and FINDER2) the adverse effect profile of the 500 mg dose was comparable to that seen with the 250 mg dose but more cases of osteoporosis (4 vs 0), vaginitis (3 vs 1) and pruritus (23 vs 8) were reported with the higher dose.

Table 3: 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.

Body system and adverse event[a]	**FASLODEX 250 mg N=423 (%)**	**Anastrozole 1 mg N=423 (%)**
Body as a whole	69.7	68.8
Asthenia	24.6	27.9
Pain	20.3	22.5
Headache	16.5	17.7
Back pain	16.1	15.4
Abdominal pain	12.8	13.2
Injection site pain*	11.3	6.9
Pelvic Pain	11.1	9.9
Chest pain	7.6	5.7
Flu syndrome	8.5	7.1
Fever	7.6	6.9
Accidental injury	5.4	6.1
Cardiovascular system	31.9	32.2
Vasodilatation	18.4	18.7
Hypertension	5.4	5.7
Digestive system	53.9	49.9
Nausea	28.1	27.0
Vomiting	15.1	12.3
Constipation	13.9	11.8
Diarrhoea	13.9	13.9
Anorexia	9.9	11.3
Haemic and lymphatic Systems	15.6	14.7
Anaemia	5.9	5.7
Metabolic and Nutritional disorders	21.5	21.0
Peripheral oedema	10.9	11.3
Musculoskeletal system	29.1	31.7
Bone pain	18.0	15.4

Body system and adverse event[a]	FASLODEX 250 mg N=423 (%)	Anastrozole 1 mg N=423 (%)
Myalgia	4.5	5.0
Arthritis	3.8	6.9
Nervous system	38.1	37.1
Dizziness	8.0	7.3
Insomnia	8.3	9.9
Paresthaesia	7.1	8.7
Depression	6.4	7.8
Anxiety	5.4	4.7
Respiratory system	40.7	35.7
Pharyngitis	17.3	12.5
Dyspnoea	16.1	13.5
Cough increased	12.3	12.1
Sinusitis	3.8	5.2
Skin and appendages	24.1	25.8
Rash	9.2	9.0
Sweating	5.2	5.7
Urogenital system	20.1	18.9
Urinary tract infection	6.9	4.7

[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.

FASLODEX has been commonly associated with elevation of liver enzymes, the vast majority <2 x ULN (frequency >1 - <10%).

DOSAGE AND ADMINISTRATION

In the absence of incompatibility studies, FASLODEX must not be mixed with other drugs. FASLODEX is not recommended for use in men.

Adult females (including the elderly)

The recommended dose (500 mg) is to be administered intramuscularly as two 5 mL injections, one in each buttock (gluteal area), at intervals of 1 month.

An additional 500 mg dose is to be given 2 weeks after the initial dose.

It is recommended that the injection be administered slowly (1-2 minutes/injection).

Caution should be taken if injecting FASLODEX at the dorsogluteal site due to the proximity of the underlying sciatic nerve.

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 further evaluated in patients with creatinine clearance less than 30 mL/min (see PRECAUTIONS).

Patients with hepatic insufficiency

No dose adjustments are recommended for patients with mild hepatic impairment. Safety and efficacy have not been further evaluated in patients with moderate to severe hepatic impairment (see PRECAUTIONS).

Elderly

No dose adjustment is required for elderly patients.

OVERDOSAGE

There is no human experience of fulvestrant overdosage. The acute toxicity of fulvestrant in laboratory animal species is low. Animal studies suggested that no effects, other than those related directly or indirectly to antioestrogenic activity, were evident with higher doses of fulvestrant. 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 fulvestrant than those recorded in patients (C_{max} >15 times). If overdose occurs, this should be managed symptomatically.

Contact the Poisons Information Centre for advice on management.

PRESENTATION AND STORAGE CONDITIONS

FASLODEX 250 mg/5 mL solution in pre-filled syringes (two (2) syringes per pack).

Each pre-filled syringe consists of:

One 5 mL clear neutral glass (Type 1) barrel containing a nominal 5 mL of FASLODEX solution for injection and fitted with a tamper evident closure. The syringes are presented in a tray with polystyrene plunger rod and a safety needle (SafetyGlide™) for connection to the barrel.

Storage Conditions

Store between 2°C–8°C (in a refrigerator).

Store in original pack.

NAME AND ADDRESS OF SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
66 Talavera Road
MACQUARIE PARK NSW 2113

Telephone: 1800 805 342

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE ARTG

6 March 2006

DATE OF MOST RECENT AMENDMENT

22 May 2017