SCHEDULING STATUS: **S 4**

1 NAME OF THE MEDICINE

FASLODEX® 250 mg solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 250 mg/5 ml (5 % m/v) fulvestrant in a long acting formulation.

This product contains 10 % m/v ethanol (96 %).
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection

Clear, colourless to yellow, viscous liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

FASLODEX is indicated for the treatment of oestrogen receptor

positive, locally advanced or metastatic breast cancer in

postmenopausal women:

- not previously treated with endocrine therapy, or
- with disease relapse on or after adjuvant anti-oestrogen therapy, or disease progression with an anti-oestrogen.

4.2 Posology and method of administration

In the absence of incompatibility studies, this medicinal product must not be mixed with other medicinal products.

Adult females (including the elderly):
The recommended dose is 500 mg to be administered intramuscularly as two 5 ml injections, one in each buttock (gluteal area), at intervals of 1 month with an additional 500 mg dose 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.
Refer to the end of this leaflet for detailed instructions for assembly, handling and disposal of the syringe and safety needle.
Children:
Not recommended for use in children or adolescents, as safety and effectiveness have not been established in this age group.
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 section 4.4).

Patients with hepatic insufficiency:

No dose adjustments are recommended for patients with mild to moderate hepatic impairment. However, as fulvestrant exposure may be increased two fold, FASLODEX should be used with caution in these patients. Safety and efficacy have not been evaluated in patients with severe hepatic impairment (See section 4.3).

Elderly:

No dose adjustment is required for elderly patients.

Interactions requiring dose adjustments:

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

4.3 Contraindications

FASLODEX is contraindicated in:

- patients with a known hypersensitivity to any of its ingredients
- patients with severe hepatic impairment
- pregnancy and women breastfeeding their infants

4.4 Special warnings and precautions for use

FASLODEX should be used with caution in patients with mild to moderate hepatic impairment (See section 5.2 and 4.2).

Caution should be used before treating patients with creatinine clearance less than 30 ml/min (See section 4.2).

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

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 section 4.2 and 4.8).

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

Special Precautions

Hypersensitivity Reactions:

Hypersensitivity reactions including angioedema and urticaria have been commonly reported (incidence of ≧ 10 %) and may be serious (see section 4.8).

Ethanol:

FASLODEX contains 10 %w/v ethanol (alcohol) as excipient,

i.e up to 500 mg per injection. This may be harmful for those suffering from alcohol dependency and should be taken into account in high risk groups such as patients with liver disease and epilepsy.

Benzyl alcohol:
FASLODEX contains benzyl alcohol as an excipient which may cause allergic reactions.

4.5 Interaction with other medicines and other forms of interaction
Fulvestrant does not significantly inhibit any of the major cytochrome P450 (CYP) isoenzymes in vitro, and results from a clinical pharmacokinetic study 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, and indirectly suggests that fulvestrant clearance would not be affected by CYP3A4 inhibitors. Results from a clinical study with ketoconazole, a potent inhibitor of CYP3A4, also indicated that there is no clinically relevant change in fulvestrant clearance. Dosage adjustment is not necessary in patients co-prescribed CYP3A4 inhibitors or inducers.

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.

4.6 Fertility, pregnancy and lactation
Studies in animals have shown reproductive toxicity.
Fulvestrant is found in rats' milk at levels significantly higher than those in rat plasma. The potential risk for humans is unknown. Therefore use of FASLODEX should be avoided in pregnant or women breastfeeding their infants. Patients of childbearing potential should use effective contraception during treatment with FASLODEX and for 2 years after the last dose.

4.7 Effects on ability to drive and use machines
FASLODEX 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.

4.8 Undesirable effects
Table 1: Summary of adverse reactions seen in clinical studies for

FASLODEX 500 mg.

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

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

[b] Based on any CT grade change from baseline.

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

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

Post-marketing side effects

Hepatobiliary disorders:

Hepatic failure and hepatitis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In the event of overdose, side effects may be exacerbated (see 4.8). There is no specific antidote. Treatment of overdose is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Endocrine therapy, Antioestrogens, ATC code: L02BA03

Fulvestrant is an anti-oestrogen. Its mode of action leads to downregulation of oestrogen receptor protein and can be described as an oestrogen receptor downregulator (ER downregulator). Fulvestrant completely blocks the trophic actions of oestrogens without itself having any partial agonist activity. Fulvestrant binds to oestrogen receptors (ERs) in a competitive manner with an affinity comparable with that of oestradiol.
Fulvestrant is a reversible inhibitor of the growth of oestrogen-sensitive human breast cancer cells *in vitro*. Fulvestrant inhibits the growth of oestrogen-sensitive human breast cancer xenografts in nude mice. Fulvestrant inhibits the growth of tamoxifen-resistant breast cancer cells in vitro and of tamoxifen-resistant breast tumours *in vivo*.

5.2 Pharmacokinetic properties

Following intravenous or intramuscular administration, fulvestrant is cleared at a rate approximating to hepatic blood flow (nominally 10,5 ml plasma/min/kg). However, FASLODEX long-acting intramuscular injection maintains plasma fulvestrant concentrations within a narrow range (up to 3-fold) over a period of at least 28 days after injection. Administration of FASLODEX 500 mg achieves exposure levels at or close to steady state within the 1st month of dosing (mean [CV]): AUC 475 (33,4 %) ng.days/ml, C_{max} 251 (35,3 %)ng/ml, C_{min} 16,3 (25,9 %) ng/ml, respectively. Results from single-dose studies of fulvestrant are predictive of multiple dose pharmacokinetics. No difference in fulvestrant pharmacokinetic profile was detected with regard to age (range 33 to 89 years).

Absorption:
Fulvestrant is not administered orally.

Distribution:
Fulvestrant's apparent volume of distribution at steady state was large (approximately 3 to 5 litre/kg), which suggests that the compound distribution is largely extravascular. Fulvestrant was highly (99 %) bound to plasma proteins at concentrations far in excess of those likely to be achieved in clinical use. 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 competitive protein binding interactions, as most reported interactions of this type involved binding to albumin and alpha-1-acid glycoproteins.

Metabolism:
Biotransformation and disposition of fulvestrant in humans have been determined following intramuscular and intravenous administration of ^{14}C-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 anti-oestrogen 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 non-P450 routes appear to be more predominant *in vivo.*

Excretion:
Fulvestrant was cleared by the hepatobiliary route, the overall rate being determined by the mode of administration. Excretion was via the faeces and renal elimination of drug-related material was negligible (less than 1 %).

Hepatic impairment
The pharmacokinetics of fulvestrant has been evaluated in a single-dose clinical study conducted in women with mild to moderate hepatic impairment (Child Pugh class A and B). A shorter duration intramuscular injection formulation was used. There was up to a 2,4-fold increase in AUC in women with hepatic impairment compared to healthy women. Women with severe hepatic impairment (Child-Pugh class C) were not evaluated.

Effects on breast cancer tissue *in vivo*
Clinical studies in postmenopausal women with primary breast cancer have shown that fulvestrant downregulates ER expression in ER

positive tumours. There was also a decrease in progesterone receptor (PR) expression (a marker of oestrogen action) consistent with the pre-clinical data demonstrating that fulvestrant lacks intrinsic oestrogen agonist activity. These changes in ER and PR expression were accompanied by reductions in expression of Ki67, a marker of tumour cell proliferation.

Effects on the postmenopausal endometrium
The pre-clinical data for fulvestrant suggest that it will not have a stimulatory effect on the postmenopausal endometrium. A study 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 oestradiol. This demonstrates a potent anti-oestrogenic effect on the postmenopausal endometrium. Neoadjuvant treatment for up to 16 weeks in breast cancer patients treated with either fulvestrant 500 mg or 250 mg did not result in clinically significant changes in endometrial thickness, indicating of a lack of agonist effect. There is no evidence of adverse endometrial effects in the breast cancer patients studied.

Effects on bone
Neoadjuvant 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 is no evidence of adverse bone effects in the breast cancer patients studied.

5.3 Preclinical safety data
Acute toxicity

The acute toxicity of 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.

Chronic toxicity
Fulvestrant 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 fulvestrant 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 fulvestrant 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.

Mutagenicity
Fulvestrant showed no genotoxic potential.

Reproductive toxicity
Fulvestrant showed effects upon reproduction and embryo/foetal development consistent with its antiestrogenic activity, at doses similar to the clinical dose. In rats, fulvestrant caused a reversible reduction in female fertility and embryonic survival at dose levels of 0.01 mg/kg/day and above, dystocia, and an increased incidence of foetal abnormalities, including tarsal flexure. Rabbits given fulvestrant at ≥ 1 mg/kg/day failed to maintain pregnancy and, at dosed up to 0.25 mg/kg/day, increases in placental weight and post-implantation loss were seen, but no effects on foetal development.

Carcinogenicity
A two-year rat oncogenicity study (intramuscular administration) showed an increased incidence of ovarian benign granulosa cell tumours in females at the high dose, 10 mg/rat/15 days. 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 antiestrogens in cycling animals. Therefore, these findings are not considered to be relevant to use of fulvestrant in postmenopausal women with advanced breast cancer.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
benzyl alcohol
benzyl benzoate
refined castor oil
ethanol (10 % m/v)

6.2 Incompatibilities
In the absence of incompatibility studies, this medicinal product must

not be mixed with other medicinal products.

6.3 Shelf life
48 months

6.4 Special precautions for storage
Store between 2 °C and 8 °C (in a refrigerator). Do not freeze. Store in the original package.
Keep out of reach of children.

6.5 Nature and contents of container
The pre-filled syringe presentation consists of 2 x 5 ml clear neutral glass (Type 1) barrels, each 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 2 safety needles (SafetyGlide™) for connection to each barrel.

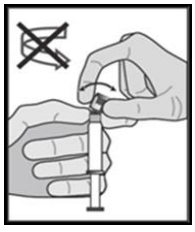
6.6 Special precautions for disposal and other handling
Instruction for administration
See section 4.2
NOTE: Due to the proximity of the underlying sciatic nerve, caution should be taken if administering FASLODEX at the dorsogluteal injection site (see section 4.4).

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.
Peel open the safety needle (SafetyGlide™) outer packaging.
Parenteral solutions must be inspected visually for particulate matter and discolouration prior to administration.

Hold the syringe upright on the ribbed part (C). hand take hold of the cap (A) and carefully tilt back and forth until the cap disconnects and can be pulled off, do not twist (see Figure 1).

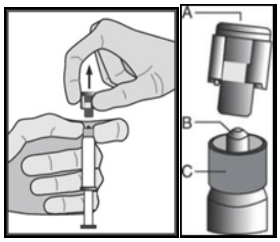
Figure 1



Remove the cap (A) in a straight upward direction. To maintain sterility do not touch the syringe tip (B) (see Figure 2).
Attach the safety needle to the syringe tip (Luer-Lok) and twist until firmly seated (see Figure 3).
Check that the needle is locked to the Luer

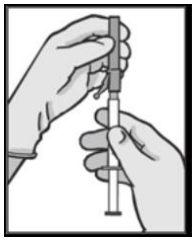
connector before moving out of the vertical plane.
Pull shield straight off needle to avoid damaging needle point. Transport filled syringe to point of administration.
Remove needle sheath.
Expel excess gas from the syringe.

Figure 2



Administer intramuscularly slowly (1-2 minutes/injection) into the buttock (gluteal area). For user convenience, the needle bevel-up position is oriented to the lever arm (see Figure 4).

Figure 3



After injection, immediately apply a single-finger stroke to the activation assisted lever arm to activate the shielding mechanism (see Figure 5).
NOTE: Activate away from self and others. Listen for click and visually confirm needle tip is fully covered.

Figure 4

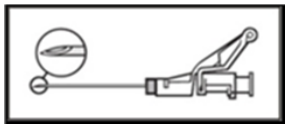
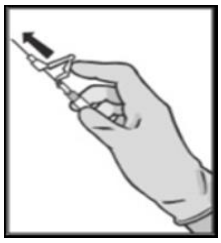


Figure 5



BD SafetyGlide™ is a trademark of Becton Dickinson and Company.
Re-order number 305917 CE marked safety needle.
Authorised Representative:
Becton Dickinson, Laagstraat 57, B9140 Temse – Belgium

7 HOLDER OF CERTIFICATE OF REGISTRATION

AstraZeneca Pharmaceuticals (Pty) Limited
Building 2, Northdowns Office Park
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2191

8 REGISTRATION NUMBER(S)

A38/21.12/0656

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 February 2006

10 DATE OF REVISION OF THE TEXT

1 April 2021

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Ref: Faslodex 250 solution for injection– EPI (30-10-2020)

CDS Jun 2019