PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

FULVEDEX 250 mg/5 ml injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 250 mg/5 ml (5 % *w/v*) fulvestrant.

FULVEDEX contains ethanol 96 % 500 mg/5 ml (10 % *w/v*) and benzyl alcohol 500 mg/5 ml (10 % *w/v*).

Sugar free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

FULVEDEX is a clear, colourless to yellow, viscous liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

FULVEDEX 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

Posology

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).

Special populations

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, FULVEDEX 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 interactions requiring dose adjustments.

Paediatric population

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

Method of administration

Administer intramuscularly slowly (1-2 minutes/injection) into the buttock (gluteal area). Caution should be taken if injecting FULVEDEX at the dorsogluteal site due to the proximity of the underlying sciatic nerve (see section 4.4).

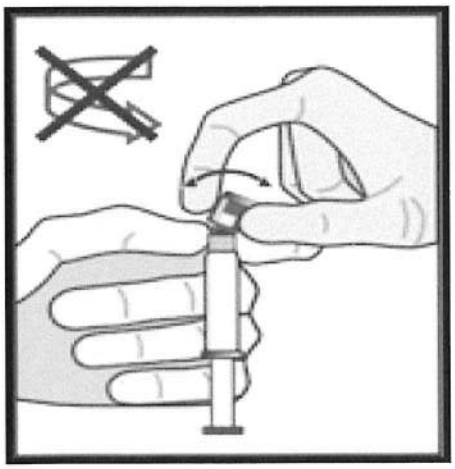
Precautions to be taken before manipulating or administering FULVEDEX

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.

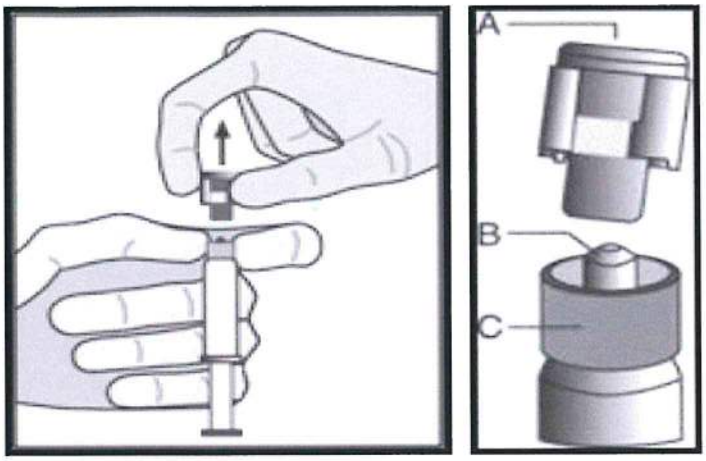
Hold the syringe upright on the ribbed part (C). With the other hand, take hold of the cap (A) and carefully tilt back and forth until the cap disconnects and can be pulled off, do not twist (see Figure 1).

Figure 1



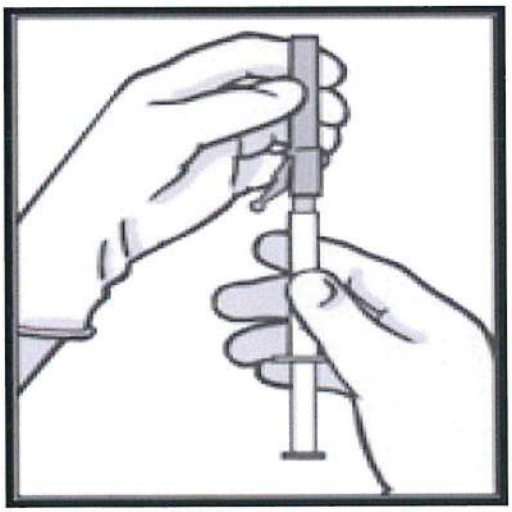
Remove the cap (A) in a straight upward direction. To maintain sterility do not touch the syringe tip (B) (see Figure 2).

Figure 2



Attach the safety needle to the syringe tip (Luer-Lok) and twist until firmly seated (see Figure 3).

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.

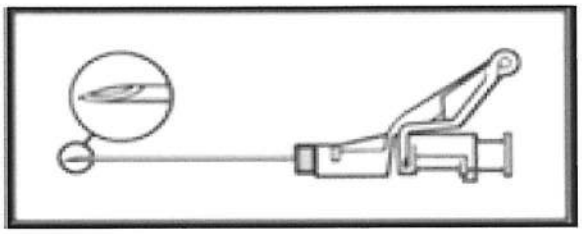
Transport filled syringe to point of administration.

Remove needle sheath.

Expel excess gas from the syringe.

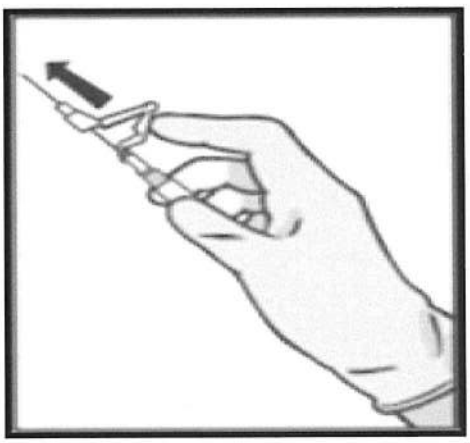
Administer intramuscularly slowly (1-2 minutes/injection) into the buttock (gluteal area). For user convenience, the needle bevel-up position is oriented to the lever arm (see Figure 4).

Figure 4



After injection, immediately apply a single-finger stroke to the activation assisted lever arm to activate the shielding mechanism (see Figure 5).

Figure 5



NOTE: Activate away from self and others. Listen for click and visually confirm needle tip is fully covered.

4.3 Contraindications

- Hypersensitivity to fulvestrant or to any of the excipients (see section 6.1).
- Severe hepatic impairment.
- Pregnancy and breastfeeding.

4.4 Special warnings and precautions for use

FULVEDEX should be used with caution in patients with mild to moderate hepatic impairment (see sections 4.2 and 5.2).

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 fulvestrant injection. Caution should be taken while administering FULVEDEX at the dorsogluteal injection site due to the proximity of the underlying sciatic nerve (see section 4.2 and 4.8).

Thromboembolic events are commonly observed in women with advanced breast cancer and have been observed in clinical studies with fulvestrant (see section 4.8). This should be taken into consideration when prescribing FULVEDEX to patients at risk.

There are 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.

Hypersensitivity reaction

Hypersensitivity reactions such as angioedema and urticaria have been frequently reported and may be serious (see section 4.8).

Interference with oestradiol antibody assays

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

Alcohol

FULVEDEX contains ethanol (alcohol) 500 mg (10 % *w/v*) per injection. This may be harmful for those suffering from alcoholism and should be considered in high-risk groups such as patients with liver disease and epilepsy.

Benzyl alcohol

FULVEDEX contains benzyl alcohol as an excipient which may cause allergic reactions.

Paediatric population

FULVEDEX is not recommended for use in children and adolescents as safety and efficacy have not been established in this group of patients (see section 5.1).

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

Women of childbearing potential

Patients of childbearing potential should use effective contraception during treatment with FULVEDEX and for 2 years after the last dose.

Pregnancy

Studies in animals have shown reproductive toxicity.

FULVEDEX should not be used during pregnancy (see section 4.3).

Breastfeeding

Fulvestrant is found in rats' milk at levels significantly higher than those in rat plasma. The potential risk for humans is unknown.

FULVEDEX should not be used whilst breastfeeding (see section 4.3).

Fertility

The effects of fulvestrant, as in FULVEDEX, on fertility in humans has not been studied.

4.7 Effects on ability to drive and use machines

FULVEDEX is unlikely to impair the ability of patients to drive or operate machinery. However, during treatment with FULVEDEX, 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

a. Summary of the safety profile

The most frequently reported adverse reactions were injection site reactions, asthenia, nausea and increased hepatic enzymes (ALT, AST, ALP).

The frequency of adverse reactions listed below is defined using the following convention: frequent; less frequent or frequency unknown (cannot be estimated from the available data).

b. Tabulated summary of adverse reactions

MedDRA system organ class	Frequency	Adverse reactions
Infections and infestations	Frequent	Urinary tract infections
Blood and lymphatic system disorders	Frequent	Reduced platelet count
Immune system disorders	Frequent	Hypersensitivity reactions: angioedema and urticaria
	Less frequent	Anaphylactic reactions
Metabolism and nutrition disorders	Frequent	Anorexia
Nervous system disorders	Frequent	Headache
Vascular disorders	Frequent	Venous thromboembolism, hot flushes
Gastrointestinal disorders	Frequent	Nausea, vomiting, diarrhoea
Hepato-biliary disorders	Frequent	Elevated liver enzymes (ALT, AST, ALP), elevated bilirubin
	Less frequent	Hepatic failure, hepatitis, elevated gamma-GT

MedDRA system organ class	Frequency	Adverse reactions
Skin and subcutaneous tissue disorders	Frequent	Rash
Musculoskeletal and connective tissue disorders	Frequent	Back pain, joint and musculoskeletal pain
Reproductive system and breast disorders	Frequent	Vaginal haemorrhage
	Less frequent	Vaginal moniliasis, leukorrhea
General disorders and administration site conditions	Frequent	Peripheral neuropathy, sciatica, injection site reaction, asthenia
	Less frequent	Injection site haemorrhage, injection site haematoma, neuralgia

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

Treatment

There is no human experience of overdosage. Animal studies suggest that no effects other than those related directly or indirectly to anti-oestrogenic activity were evident with higher doses of fulvestrant, as in FULVEDEX. If overdose occurs, this should be managed symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.21.12 Hormone inhibitors

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, fulvestrant 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 fulvestrant 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.

Biotransformation

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 sulfoxide.

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*.

Elimination

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol 96 %

Benzyl alcohol

Benzyl benzoate

Castor oil

Nitrogen (E941)

6.2 Incompatibilities

In the absence of compatibility studies FULVEDEX must not be mixed with other medicines.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store between 2 °C and 8 °C (in a refrigerator). Do not freeze. Protect from light. Store in the original carton until time of use.

6.5 Nature and contents of container

The pre-filled syringe presentation consists of 2 x 5 ml colourless, transparent pre-filled syringe barrels made of borosilicate glass (Type I), with a luer tip and a tip cap. It contains a grey fluoropolymer coated bromobutyl rubber plunger (5 ml). The two (2) syringes are presented in a tray with a plunger rod and fitted with a backstop. Two (2) safety needles (SafetyGlide) for connection to each barrel are also provided.

All of the above is kept in a carton to prevent light exposure.

6.6 Special precautions for disposal and other handling

Pre-filled syringes are for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Kahma Biotech (Pty) Ltd

106, 16th Road

Midrand

1686

South Africa

8 REGISTRATION NUMBER(S)

550531

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8 November 2022

10 DATE OF REVISION OF THE TEXT

Not applicable