Proposed Professional Information

SHEDULING STATUS

S4

1. NAME OF THE MEDICINE

FUVISTRA 250 mg/5 ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Ethanol (96 %): 10 % *m/v*

Benzyl Alcohol: 10 % *m/v*

Sugar free

Benzyl Benzoate: 150mg/ml (750mg per injection)

For full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Solution for injection

Clear colourless to yellow viscous solution, free from visible particles filled in 5 ml pre filled glass syringe.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FUVISTRA is indicated for the treatment of estrogen 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-estrogen therapy, or disease progression with an anti-estrogen.

4.2. Posology and method of administration

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

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.

Method of administration

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

Caution should be taken if injecting **FUVISTRA** 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.

Special Populations

Patients with renal insufficiency:

No dose adjustments are recommended for patients with a creatinine clearance greater than 30 ml/min. Safely 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.

FUVISTRA 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.

Paediatric population:

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

Interactions requiring dose adjustments:

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

4.3. Contraindications

FUVISTRA is contraindicated in

- patients with a known hypersensitivity to fulvestrant or to any of the excipients listed in section 6.1
- patients with severe hepatic Impairment
- pregnancy and women breastfeeding their infants

4.4. Special warnings and precautions for use

FUVISTRA should be used with caution in patients with mild to moderate hepatic impairment (See **section 4.2**).

Caution should be used before treating patients with severe renal impairment (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 intramuscular route of administration.

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

Injection site related events including sciatica, neuralgia, neuropathic pain, and peripheral neuropathy have been reported with fulvestrant injection. Caution should be taken while administering **FUVISTRA** at the dorsogluteal injection site due to the proximity of the underlying sciatic nerve (see **section 4.2** and **section 4.8**).

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

The efficacy and safety of fulvestrant (either as monotherapy or in combination with palbociclib) have not been reported in patients with critical visceral disease.

When fulvestrant is combined with palbociclib, please also refer to the Professional Information of palbociclib.

Interference with estradiol antibody assays

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

Special Precautions

Hypersensitivity Reactions:

Hypersensitivity reactions such as angioedema and urticaria have been frequently reported (incidence of 1·10 %) and may be serious (see **section 4.8**).

Paediatric population

Fulvestrant is not recommended for use in children and adolescents as safety and efficacy have not been reported in this group of patients.

Ethanol

FUVISTRA contains 500 mg of alcohol (ethanol) in each 5 ml pre-filled glass syringe. The amount in 5 ml of this injection is equivalent to 10 ml beer or 4 ml wine.
This may be harmful for those suffering from alcoholism and should be taken into account in high risk groups such as patients with liver disease and epilepsy.

Benzyl alcohol

FUVISTRA contains 500 mg benzyl alcohol in each 5 ml pre-filled glass syringe. Benzyl alcohol 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 reported clinical pharmacokinetic study involving co-administration of fulvestrant with midazolam also suggested that therapeutic doses of fulvestrant will have no inhibitory effects on CYP3A4. In addition, although fulvestrant can be metabolised by CYP3A4 *in vitro*, a reported clinical study with rifampicin reported 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 reported 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 estradiol, fulvestrant may interfere with antibody-based estradiol assays and may result In falsely increased levels of estradiol. (See section 4.4)

4.6. Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

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

Pregnancy

Fulvestrant is contraindicated in pregnancy (see **section 4.3**). Fulvestrant has been reported to cross the placenta after single intramuscular doses in rat and rabbit. Studies in animals have reported reproductive toxicity including an increased incidence of foetal abnormalities and deaths. If pregnancy occurs while taking fulvestrant, the patient must be informed of the potential hazard to the foetus and potential risk for loss of pregnancy.

Breastfeeding

Breast-feeding must be discontinued during treatment with fulvestrant. Considering the potential for serious adverse reactions due to fulvestrant in pregnant, breast-fed infants, use during lactation is contraindicated (see **section 4.3**).

Fertility

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

4.7. Effects on ability to drive and use machines

FUVISTRA is unlikely to impair the ability of patients to drive or operate machinery. However, during treatment with **FUVISTRA**, asthenia has been reported and caution should be observed by those patients who experience this symptom when driving or operating machinery (see **section 4.8**).

4.8. Undesirable effects

Summary of the safety profile

Monotherapy

This section provides information based on all adverse reactions from reported clinical studies, post-marketing studies or spontaneous reports. In the pooled dataset of fulvestrant monotherapy, the most frequently reported adverse reactions were injection site reactions, asthenia, nausea, and increased hepatic enzymes (ALT, AST, ALP).

System Organ Class	**Frequency**	**Adverse Reaction**
Infections and infestations	Frequent	Urinary tract infections
Blood and lymphatic system	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	Hot flushes Venous thromboembolism
Gastrointestinal disorders	Frequent	Nausea, vomiting, diarrhoea
Hepatobiliary disorders	Frequent	Elevated bilirubin, elevated liver enzymes (ALT, AST, ALP)
	Less Frequent	Elevated gamma-GT, Hepatic failure, hepatitis
Skin and subcutaneous tissue disorders	Frequent	Rash
Musculoskeletal and connective tissue disorders	Frequent	Joint and musculoskeletal pain, back pain
Reproductive system and	Frequent	Vaginal haemorrhage

breast disorders	Less Frequent	Vaginal moniliasis, leukorrhea
General disorders and administration site conditions	Frequent	Injection site reactions, asthenia, neuropathy peripheral, sciatica
	Less frequent	Injection site haemorrhage, injection site haematoma, neuralgia

Description of selected adverse reactions

The descriptions included below are based on reported safety analysis set of patients who received at least one (1) dose of fulvestrant and patients who received at least one (1) dose of anastrozole, respectively in a reported Phase 3 study.

Joint and musculoskeletal pain

In the reported study, the number of patients who reported an adverse reaction of joint and musculoskeletal pain was 31,2 % and 24,1 % for fulvestrant and anastrozole arms, respectively. Of the patients in the fulvestrant arm, 40 % of patients reported joint and musculoskeletal pain within the first month of treatment, and 66,2 % of patients within the first 3 months of treatment. No patients reported events that were CTCAE Grade ≥ 3 or that required a dose reduction, dose interruption, or discontinued treatment due to these adverse reactions.

Combination therapy with palbociclib

The overall safety profile of fulvestrant when used in combination with palbociclib is based on reported data from patients with HR-positive, HER2-negative advanced or metastatic breast cancer in the randomised 3 study. The most frequent (≥ 20 %) adverse reactions of any grade reported in patients receiving fulvestrant in combination with palbociclib were neutropenia, leukopenia, infections, fatigue, nausea, anaemia, stomatitis, diarrhoea, thrombocytopenia and vomiting. The frequent (≥ 2 %) Grade ≥ 3 adverse reactions were neutropenia, leukopenia, infections, anaemia, AST increased, thrombocytopenia, and fatigue.

Description of selected adverse reactions

Neutropenia

In patients receiving fulvestrant in combination with palbociclib in the reported study, neutropenia of any grade was reported in 84,1 % patients, with Grade 3 neutropenia being reported in 58,0 % patients, and Grade 4 neutropenia being reported in 11,6 % patients. In the fulvestrant + placebo arm, neutropenia of any grade was reported in 3,5 % patients. There were no reports of Grade 3 and 4 neutropenia in the fulvestrant + placebo arm.

In patients receiving fulvestrant in combination with palbociclib, the median time to first episode of any grade neutropenia was 15 days (range: 13 - 512 days) and the median duration of Grade ≥3 neutropenia was 16 days. Febrile neutropenia has been reported in 3 (0,9 %) patients receiving fulvestrant in combination with palbociclib.

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**

Reaction Reporting form', found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/index/8

4.9. Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification

Pharmacotherapeutic group: Endocrine therapy, Anti~~o~~estrogens, ATC code: L02BA03

A. 21.12 Hormone inhibitors

Pharmacodynamic properties:

Fulvestrant is an anti-estrogen. Its mode of action leads to downregulation of ~~o~~estrogen receptor protein and can be described as an estrogen receptor downregulator (ER downregulator). Fulvestrant completely blocks the trophic actions of estrogens without itself having any partial agonist activity. Fulvestrant binds to ~~o~~estrogen receptors (ERs) in a competitive manner with an affinity comparable with that of estradiol.

Fulvestrant is a reversible inhibitor of the growth of ~~o~~estrogen-sensitive human breast cancer cells *in vitro*. Fulvestrant inhibits the growth of estrogen-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 alter 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 reported single-dose studies of fulvestrant are predictive of multiple dose pharmacokinetics.

No difference in fulvestrant pharmacokinetic profile was reported 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 reported to be large (approximately 3 to 5 litre/ kg), which suggests that the compound distribution is largely extravascular. Fulvestrant was reported to be 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 have been reported 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 reported 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 have been reported to yield 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-estrogen models. Reported 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 has been reported to be cleared by the hepatobiliary route, the overall rate being determined by the mode or 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 reported 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.

<u>Environmental Risk Assessment (ERA)</u>

Environmental risk assessment studies have reported that fulvestrant may have potential to cause adverse effects to the aquatic environment (see **section 6.6**).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol 96 % (alcohol) (Emprove), Benzyl alcohol (Parenteral Grade), Benzyl Benzoate, Castor oil Refined, Nitrogen.

6.2 Incompatibilities

Not known

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 original package.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

2 x 5 ml pre-filled syringes packed in a lidded tray with two needles in a printed carton.

6.6 Special precautions for disposal and other handling

Instructions for administration

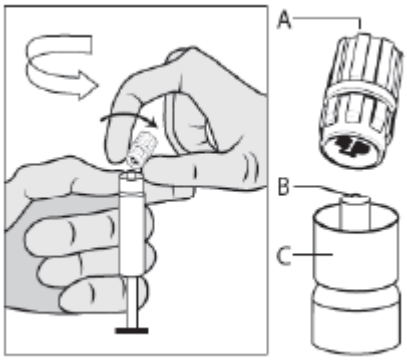
Administer the injection according to the local guidelines for performing large volume intramuscular injections.

NOTE: Due to the proximity of the underlying sciatic nerve, caution should be taken if administering fulvestrant 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.

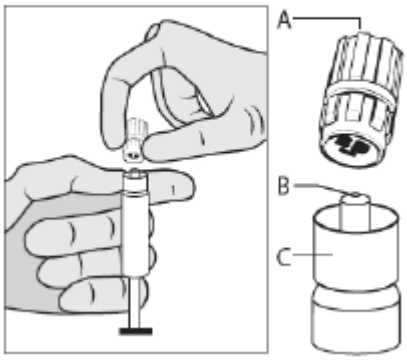
For each of the two syringes:

- 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 twist the PRTC (Plastic Rigid Tip cap) in anticlockwise direction.



- Remove the PRTC 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 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 3

- 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).

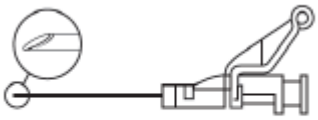


Figure 4

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

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

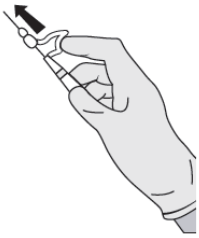
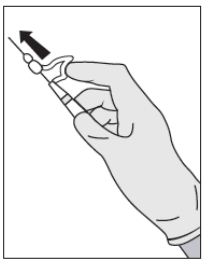


Figure 5



Disposal

Pre-filled syringes are for single use **only**.

This medicine may pose a risk to the aquatic environment.

Return all unused or expire medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewerage systems (e.g. toilets).

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill, Ext. 1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER(S)

56/21.12/0245

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

25 June 2024

10. DATE OF REVISION OF THE TEXT

25 June 2024