SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ERANFU™ 250 solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 250 mg / 5 mL fulvestrant in a long acting formulation.

Excipients with known effect (per 5 ml):

Alcohol (Ethanol) (96 %, 500 mg)

Benzyl alcohol (500 mg)

Benzyl benzoate (750 mg)

For the 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

ERANFU™ 250 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 on therapy with an anti-oestrogen.

4.2 Posology and method of administration

Posology

Adult females (including the elderly):

The recommended dose is 500 mg intramuscularly at intervals of 1 month with an additional 500 mg dose given two weeks after the initial dose.

Special populations

Renal impairment:

No dosage adjustments are recommended for patients with mild to moderate renal impairment (i.e. patients having a creatinine clearance greater than 30 ml/min).

Safety and efficacy have not been evaluated in patients with severe renal impairment (creatinine clearance < 30 ml/min), and, therefore, caution is recommended in these patients (see Section 4.4).

Hepatic impairment:

No dose adjustments are recommended for patients with mild to moderate hepatic impairment. However, as fulvestrant exposure may be increased, ERANFU™ 250 should be used with caution in these patients.

Safety and efficacy have not been evaluated in patients with severe hepatic impairment (see

Sections 4.3, 4.4 and 5.2).

Elderly:

No dose adjustment is required for elderly patients.

Interactions requiring dose adjustment:

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

Children:

ERANFU™ 250 is not recommended for use in children or adolescents, as safety and efficacy have not been established in this age group.

Method of administration

ERANFU™ 250 should be administered as two consecutive 5 ml injections by slow intramuscular injection (1 to 2 minutes/injection), one in each buttock (gluteal area).

Caution should be taken if injecting ERANFU™ 250 at the dorso-gluteal site due to the proximity of the underlying sciatic nerve.

Refer to the end of the leaflet. For detailed instructions on administration, see Section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance (fulvestrant) or to any of the excipients (see Section 6.1).
- Patients with severe hepatic impairment (see Sections 4.4 and 5.2).
- Pregnancy and lactation (see Section 4.6).

4.4 Special warnings and precautions for use

- ERANFU™ 250 should be used with caution in patients with mild to moderate hepatic impairment (see Sections 4.2, 4.3 and 5.2).
- ERANFU™ 250 should be used with caution before treating patients with severe renal impairment (creatinine clearance less than 30 ml/min) (see Sections 4.2 and 5.2).
- Due to the intramuscular route of administration, caution should be used if treating patients with bleeding diatheses or thrombocytopenia or patients taking anticoagulants.
- Thromboembolic events are commonly observed in women with advanced breast cancer and have been observed in clinical trials with fulvestrant (see Section 4.8). This should be taken into consideration when prescribing ERANFU™ 250 to patients at risk.
- Injection site related events including sciatica, neuralgia, neuropathic pain and peripheral neuropathy have been reported with fulvestrant. Caution should be taken while administering ERANFU™ 250 at the dorso-gluteal injection site due to the proximity of the underlying sciatic nerve (see Sections 4.2 and 4.8).
- 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.

- The efficacy and safety of fulvestrant has not been studied in patients with critical visceral disease.
- Hypersensitivity reactions such as angioedema and urticaria have been commonly reported with fulvestrant (incidence of 1 to 10 %) and may be serious (see Section 4.8).

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 (see Section 4.5).

Ethanol

- ERANFU™ 250 contains 10 % w/v ethanol (alcohol) as an excipient, i.e. up to 500 mg per injection, 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

- ERANFU® 250 contains benzyl alcohol as an excipient which may cause allergic reactions.

<u>Paediatric population:</u>

- ERANFU™ 250 is not recommended for use in children and adolescents as safety and efficacy have not been established in this group of patients.

4.5 Interaction with other medicines and other forms of interaction

A clinical interaction study with midazolam (substrate of CYP3A4) demonstrated that fulvestrant does not inhibit CYP3A4. Clinical interaction studies with rifampicin (inducer of CYP3A4) and ketoconazole (inhibitor of CYP3A4) showed no clinically relevant change in fulvestrant clearance. Dose adjustment is therefore not necessary in patients who are receiving fulvestrant and CYP3A4 inhibitors or inducers concomitantly.

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:

Patients of child-bearing potential should be advised to use effective contraception while on treatment with ERANFU™ 250 and for two years after last dose.

Pregnancy:

ERANFU™ 250 is contraindicated in pregnancy (see Section 4.3). Fulvestrant has been shown to cross the placenta after single intramuscular doses in rat and rabbit. Studies in animals have shown reproductive toxicity, including an increased incidence of foetal abnormalities and deaths. If pregnancy occurs while taking ERANFU™ 250, the patient must be informed of the potential hazard to the foetus and potential risk for loss of pregnancy.

Lactation:

Breast-feeding must be discontinued during treatment with ERANFU™ 250. Fulvestrant is excreted in rat's milk. It is not known if fulvestrant is excreted in human milk. Considering the

potential for serious adverse reactions due to fulvestrant in breast-fed infants, ERANFU™ 250 Is contraindicated during lactation] (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

ERANFU™ 250 has no or negligible influence on the ability to drive or operate machinery. However, since asthenia has been reported during treatment with fulvestrant, caution should be observed by those patients who experience this adverse reaction when driving or operating machinery (see Section 4.8).

4.8 Undesirable effects

Summary of the safety profile

This section provides information based on all adverse reactions from 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).

Table 1: Adverse reactions by system organ class and frequency

System Organ Class	Frequent	Less frequent
Infections and infestations	Urinary tract infections	
Blood and lymphatic system disorders	Reduced platelet count	

Immune System disorders	Hypersensitivity reactions (angioedema, urticaria)	Anaphylactic reactions
Metabolism and nutrition disorders	Anorexia	
Nervous system disorders	Headache	
Vascular disorders	Hot flushes, venous thromboembolism	
Gastrointestinal disorders	Nausea, vomiting, diarrhoea	
Hepatobiliary disorders	Increased hepatic enzymes (ALT, AST, ALP), elevated bilirubin	Hepatic failure, hepatitis, elevated gamma-GT
Skin and subcutaneous tissue disorders	Rash	
Musculoskeletal and connective tissue disorders	Joint and musculoskeletal pain e.g. arthralgia, myalgia, back pain	
Reproductive system and breast disorders	Vaginal haemorrhage	Vaginal moniliasis, leukorrhoea
General disorders and administration site conditions	Asthenia, injection site reactions, neuropathy peripheral, sciatica	Injection site haemorrhage, injection site haematoma, neuralgia

Joint and musculoskeletal pain

In the FALCON study, of the 65 patients in the fulvestrant arm who reported joint and musculoskeletal pain, 40 % (26/65) of patients reported joint and musculoskeletal pain within the first month of treatment, and 66,2 % (43/65) 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.

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

There is no experience of overdose in humans. Animal studies suggest that no effects other than those related directly or indirectly to anti-oestrogenic activity were evident with higher doses of fulvestrant. Should overdose occur, symptomatic supportive treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Fulvestrant is a steroidal anti-oestrogen. It is a competitive oestrogen receptor (ER) antagonist with an affinity comparable to oestradiol. Fulvestrant completely blocks the tropic actions of oestrogens without itself having any partial agonistic activity. Its mechanism of action leads to down regulation of oestrogen receptor protein and can be described as an oestrogen receptor down regulator (ER down regulator).

Fulvestrant is a reversible inhibitor of the growth of oestrogen-sensitive human breast cancer cells *in vitro*. Fulvestrant inhibit the growth of oestrogen-sensitivite human breast cancer xenografts in nude mice. Fulvestrant inhibit the growth of tamoxifen resistant breast cancer cells

in vitro and of tamoxifen resistant breast tumours *in vivo.*

Effect on breast cancer tissue in vivo

Clinical trials 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 preclinical data demonstrating that fulvestrant lacks intrinsic oestrogen activity. These changes in ER and PR expression were accompanied by reductions in expression of Ki67, marker of tumour cell proliferations.

Effect on 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 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 results in clinically significant changes in endometrial thickness, indicating a lack of agonistic effects. 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 fulvestrant 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.

5.2 Pharmacokinetic properties

Absorption:

After administration of fulvestrant long-acting intramuscular injection, it is slowly absorbed and maximum plasma concentrations (C_{max}) are reached after about 5 days. Administration of fulvestrant 500 mg regimen 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). At steady state, fulvestrant plasma concentrations are maintained within a relatively narrow range with up to an approximately 3-fold difference between maximum and trough concentrations. After intramuscular administration, the exposure is approximately dose proportional in the dose range 50 to 500 mg.

Distribution:

Fulvestrant is subject to extensive and rapid distribution. The large apparent volume of distribution at steady state (Vdss) of approximately 3 to 5 l/kg suggests that 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. No interaction studies were conducted on competitive protein binding. The role of sex hormone-binding globulin (SHBG) has not been determined.

Biotransformation:

The metabolism of fulvestrant has not been fully evaluated; however, it involves combinations of a number of possible biotransformation pathways analogous to those of endogenous steroids. Identified metabolites (includes 17-ketone, sulphone, 3-sulphate, 3- and 17-glucuronide 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*. *In vitro* data suggest that fulvestrant does not inhibit CYP450 isoenzymes.

Elimination:

Fulvestrant is eliminated mainly in a metabolised form. The major route of excretion is via the faeces. Less than 1 % is excreted in the urine. Fulvestrant has a high clearance of 11±1,7 ml/min/kg. This suggests a high hepatic extraction ratio. The terminal half-life ($t_{1/2}$) after intramuscular administration is governed by the absorption rate and was estimated to be 50 days.

Special populations:

In a population pharmacokinetic analysis of data from phase III studies, no difference in fulvestrant's pharmacokinetic profile was detected with regard to age (range 33 to 89 years), weight (40 to127 kg) or race.

Renal impairment

The pharmacokinetics of fulvestrant, to any clinically relevant extent, was not influenced by mild to moderate impairment of renal function.

Hepatic impairment

The pharmacokinetics of fulvestrant has been evaluated in a single dose clinical trial conducted in subjects 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 2,5 -fold increase in AUC in subjects with hepatic impairment compared to healthy subjects.
Subjects with severe hepatic impairment (Child Pugh class C) were not evaluated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Alcohol (Ethanol – 96 %)

Benzyl alcohol

Benzyl benzoate

Castor oil.

6.2 Incompatibilities

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

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator between 2 °C and 8 °C.

Temperature excursions outside 2 °C to 8 °C should be limited. This includes avoiding storage at temperatures exceeding 30 °C, and not exceeding a 28-day period where the average storage temperature for the product is below 25°C (but above 2 °C to 8 °C). After temperature excursions, the product should be returned immediately to the recommended storage conditions (store and transport in a refrigerator 2 °C to 8 °C). Temperature excursions have a cumulative effect on the product quality and the 28-day time period must not be exceeded over the duration of the 2-year shelf life of ERANFU™ 250. Exposure to temperatures below 2 °C will not damage the product providing it is not stored below -20 °C.

Do not freeze.

Keep the pre-filled syringes in the original packaging, in order to protect from the light.

6.5 Nature and contents of container

The pre-filled syringe presentation consists of two 5 ml Clear Type - I glass barrels without graduation and with OVS Tip Cap, each containing 250 mg/5 ml of fulvestrant solution.

The pre-filled syringes are stoppered with grey colour bromobutyl plunger stoppers with fluorotec lamination.

The syringes are presented in tray with clear polystyrene plunger rods with two safety needles (Safetyglide™) with Plastic Needle Shield.

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 ERANFU™ 250 at the dorso-gluteal injection site (see Section 4.4).

Warning - Do not autoclave safety needle (BD Safety Glide™ 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).

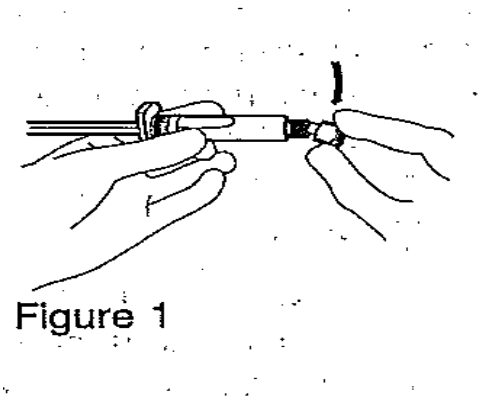

Figure 1

• 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).

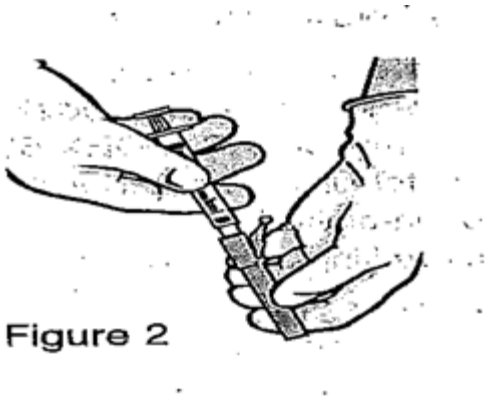
Figure 2

Twist until firmly seated.

• Pull shield straight off needle to avoid damaging needle point.

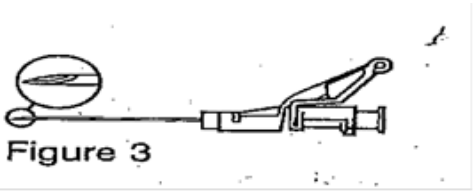
Figure 3

• Transport filled syringe to point of administration.

• Remove needle sheath.

• Parenteral solutions must be inspected visually for particulate matter and discolouration 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).

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

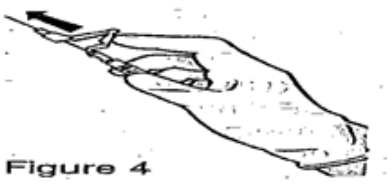
Figure 4

NOTE: Activate away from self and others.

Listen for click and visually confirm needle tip

fully covered.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8. REGISTRATION NUMBER(S)

51/21.12/0740

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 May 2020