FINAL PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

FULDEXA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients: Alcohol 96 %, benzyl alcohol, castor oil and benzyl benzoate.

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection

A clear, colorless to yellow, viscous solution, filled in a clear glass pre-filled syringe. When examined under suitable conditions of visibility it should be practically free from foreign particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FULDEXA is indicated for 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.

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4.2 Posology and method of administration

In the absence of incompatibility studies, FULDEXA must not be mixed with other medicines.

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). Caution should be taken if injecting 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. 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, FULDEXA 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.

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Interactions requiring dose adjustments

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

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

Intramuscular injection.

4.3 Contraindications

FULDEXA is contraindicated in:

- patients with a known hypersensitivity to fulvestrant or 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

FULDEXA should be used with caution in patients with mild to moderate hepatic impairment (see sections 4.2, 4.3 and 5.2).

FULDEXA should be used with caution in patients with severe renal impairment (creatinine clearance less than 30 ml/min).

Due to the intramuscular route of administration, FULDEXA should be used with caution if treating patients with bleeding diatheses, thrombocytopenia or those taking anticoagulant treatment.

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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 FULDEXA 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 FULDEXA at the dorsogluteal 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 FULDEXA (either as monotherapy or in combination with palbociclib) have not been studied in patients with critical visceral disease.

When FULDEXA is combined with palbociclib, please also refer to the professional information of palbociclib.

Hypersensitivity Reactions

Hypersensitivity reactions including angioedema and urticaria have been reported 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.

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Ethanol

FULDEXA contains 10 % w/v ethanol (alcohol 96 %) 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

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

Castor oil

May cause severe allergic reactions

Paediatric population

FULDEXA 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 medicinal products 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 oestradiol, fulvestrant may interfere with antibody-based oestradiol assays and may result in falsely increased levels of oestradiol.

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4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

FULDEXA 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 FULDEXA, the patient must be informed of the potential hazard to the foetus and potential risk for loss of pregnancy.

Breastfeeding

Breastfeeding must be discontinued during treatment with FULDEXA. Fulvestrant is excreted in milk in lactating rats. It is not known whether fulvestrant is excreted in human milk. Considering the potential for serious adverse reactions due to fulvestrant in breast-fed infants, use during lactation is contraindicated (see section 4.3).

Fertility

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

4.7 Effects on ability to drive and use machines

FULDEXA has no or negligible influence on the ability to drive or use machines. However, since asthenia has been reported with FULDEXA, caution should be observed by those patients who experience this adverse reaction when driving or operating machinery.

4.8 Undesirable effects

a. Summary of the safety profile

Monotherapy

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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).

b. Tabulated list of adverse reactions

Table 1 below contains adverse reactions associated with fulvestrant treatment.

Table 1: ADRs reported in patients treated with FULDEXA monotherapy

SYSTEM ORGAN CLASS	INCIDENCE	ADVERSE REACTION
Infections and infestations	Frequent	Urinary tract infections
Blood and lymphatic system disorders	Frequent	Reduced platelet count [e]
Immune system disorders	Frequent	Hypersensitivity reactions[e], angioedema and urticaria
	Less frequent	Anaphylactic reactions
Metabolism and nutrition disorders	Frequent	Anorexia[a]
Nervous system disorders	Frequent	Headache
Vascular disorders	Frequent	Hot flushes[e]
	Frequent	Venous thromboembolism[a]
Gastrointestinal disorders	Frequent	Nausea
	Frequent	Vomiting, diarrhoea
Hepatobiliary disorders	Frequent	Elevated hepatic enzymes (ALT, AST, ALP)[a]
	Frequent	Elevated bilirubin[a]
	Less frequent	Hepatic failure[c, f], hepatitis[f], elevated gamma-GT[f]

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Skin and subcutaneous tissue disorders	Frequent	Rash[e]
Musculoskeletal and connective tissue disorders	Frequent	Joint and musculoskeletal pain[d]
	Frequent	Back pain [a]
Reproductive system and breastdisorders	Frequent	Vaginal haemorrhage[e]
	Less frequent	Vaginal moniliasis [f], leukorrhea [f]
General disorders and administration site conditions	Frequent	Asthenia[a], injection site reactions[b]
	Frequent	Neuropathy peripheral[e], sciatica[e]
	Less frequent	Injection site haemorrhage [f], injection sitehaematoma [f], neuralgia [c,f]

a: Includes adverse drug reactions for which the exact contribution of FULDEXA cannot be assessed due to the underlyingdisease.

b: The term injection site reactions does not include the terms injection site haemorrhage, injection site haematoma,sciatica, neuralgia and neuropathy peripheral.

c: The event was not observed in major clinical studies (CONFIRM, FINDER 1, FINDER 2, NEWEST).

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

e: Frequency category differs between pooled safety dataset and FALCON.

f: ADR was not observed in FALCON

c. Description of selected adverse reactions

Neutropenia

In patients receiving fulvestrant in combination with palbociclib in the 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.

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In patients receiving fulvestrant in combination with palbociclib, the median time to first episode of any grade neutropeniawas 15 days (range: 13 – 512 days) and the median duration of Grade ≥ 3 neutropenia was 16 days. Febrile neutropenia has been reported in 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. Healthcare professionals 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 can be precipitated and/or be of increased severity (see section 4.8). There is no specific antidote. Treatment of overdose is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A. 21.12 Hormone inhibitors

Pharmacotherapeutic group: Endocrine therapy, Antioestrogens

ATC code: L02BA03

Mechanism of action

Fulvestrant is a competitive oestrogen receptor (ER) antagonist with an affinity comparable to oestradiol. Fulvestrant blocks the trophic actions of oestrogens without any partial agonist (oestrogen-like) activity. The mechanism of action is associated with downregulation of oestrogen receptor protein levels.

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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*.

Clinical studies in postmenopausal women with primary breast cancer have shown that fulvestrant significantly down regulates ER protein in ER positive tumours compared with placebo. There was also a significant decrease in progesterone receptor expression consistent with a lack of intrinsic oestrogen agonist effects. It has also been shown that fulvestrant 500 mg downregulates ER and the proliferation marker Ki67, to a greater degree than fulvestrant 250 mg in breast tumours in postmenopausal neoadjuvant setting.

5.2 Pharmacokinetic properties

Absorption

Fulvestrant is not administered orally.

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.

Metabolism

Biotransformation and disposition of fulvestrant in humans have been determined following intramuscular and intravenous administration of ^{14}C-labelled fulvestrant.

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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*.

Elimination

Fulvestrant is eliminated mainly in metabolised form. Fulvestrant was cleared by the hepatobiliary route, the overall rate being determined by the mode of administration. 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. The terminal half-life (t1/2) after intramuscular administration is governed by the absorption rate and was estimated to be 50 days.

Special populations

Renal impairment

Mild to moderate impairment of renal function did not influence the pharmacokinetics of fulvestrant to any clinically relevant extent.

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 high dose of a shorter duration intramuscular injection formulation was used. There was up to about 2.5-fold increase in AUC in women with hepatic impairment compared to healthy subjects. In patients administered fulvestrant, an increase in exposure of this magnitude is expected to be well tolerated. Women with severe hepatic impairment (Child-Pugh class C) were not evaluated.

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Paediatric population

The pharmacokinetics of fulvestrant has been evaluated in a clinical study conducted in 30 girls with Progressive Precocious Puberty associated with McCune Albright Syndrome. The paediatric patients were aged 1to 8 years and received 4 mg/kg monthly intramuscular dose of fulvestrant. The geometric mean (standard deviation) steady state trough concentration (Cmin,ss) and AUCss was 4.2 (0.9) ng/mL and 3680 (1020) ng*hr/mL, respectively. Although the data collected were limited, the steady-state trough concentrations of fulvestrant in children appear to be consistent with those in adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol (96 %)

Benzyl alcohol

Benzyl benzoate

Refined 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

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

6.4 Special precautions for storage

Temperature excursions outside 2 °C – 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 – 8 °C). After temperature excursions, the product should be returned immediately to the recommended storage conditions (store and transport in a refrigerator 2 °C – 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 FULDEXA (see section 6.3). Exposure to temperatures below 2 °C will not damage the product providing it is not stored below -20 °C.

Store the pre-filled syringe in the original package in order to protect from light.

6.5 Nature and contents of container

The pre-filled syringe presentation consists of:

Glass Syringe with plunger rod plugged with plunger stopper containing 5 ml of fulvestrant solution for injection.

Pack size: 1 or 2 pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Recommendations for safe 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 FULDEXA at the dorsogluteal injection site (see section 4.4).

Warning - Do not autoclave safety needle (BD SafetyGlide Shielding Hypodermic Needle) before use.

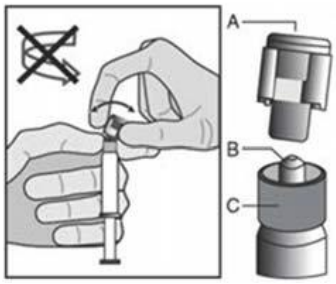
Hands mustremain behind the needle at all times during use and disposal.

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For each of the two syringes:

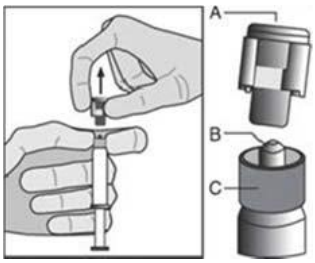
- Remove glass syringe barrel from tray and check that it is not damaged.
- Peel open the safety needle (SafetyGlide) outer packaging.
- Parenteral solutions must be inspected visually for particulate matter anddiscolouration prior to administration.
- Hold the syringe upright on the ribbed part (C). With the other hand, takehold of the cap (A) and carefully tilt back and forth until the cap disconnectsand can be pulled off, do not twist (see Figure 1).

Figure 1



- Remove the cap (A) in a straight upward direction. To maintain sterility donot touch the syringe tip (B) (see Figure 2).

Figure 2

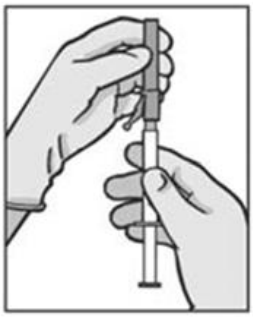


- Attach the safety needle to the Luer-Lok and twist until firmly seated (see Figure 3).
- Check that the needle is locked to the Luer connector before moving out ofthe vertical plane.
- Pull shield straight off needle to avoid damaging needle point.
- Transport filled syringe to point of administration.

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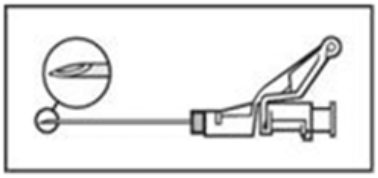
- Remove needle sheath.
- Expel excess gas from the syringe.

Figure 3



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

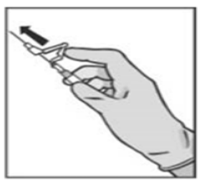
Figure 4



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

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

Figure 5



Disposal

Pre-filled syringes are for single use only.

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This medicine may pose a risk to the aquatic environment. Any unused medicinal product or waste material should bedisposed of in accordance with local requirements (see section 5.3).

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Tuscany Office Park, Building 2,

6 Coombe Place,

Rivonia,

Johannesburg

South Africa

8. REGISTRATION NUMBER(S)

55/21.12/0762

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01 November 2022

10. DATE OF REVISION OF THE TEXT

To be confirmed.