1.3.1.1 Approved Professional Information for Medicines for Human Use

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

VESOTA Solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VESOTA solution for injection:

Each pre-filled syringe contains 250 mg/5 mL fulvestrant.

Excipients with known effect (per 5 mL):

Ethanol 96 %: 500 mg

Benzyl alcohol: 500 mg

Benzyl benzoate: 750 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to yellow, viscous solution essentially free from visible particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

VESOTA 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-estrogen.

4.2. Posology and method of administration

Posology

Adult females (including the elderly):

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

Special populations

Patients with renal impairment:

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 impairment:

No dose adjustments are recommended for patients with mild to moderate hepatic impairment. However, as fulvestrant exposure may be increased two fold, VESOTA 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 population:

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.

Method of administration

VESOTA should be administered as two consecutive 5 mL injections by slow intramuscular injection (1-2 minutes/injection), one in each buttock (gluteal area).

Caution should be taken if injecting VESOTA at the dorsogluteal site due to the proximity of the underlying sciatic nerve.

For detailed instructions for assembly, handling and disposal, see section 6.6.

4.3. Contraindications

VESOTA is contraindicated in:

- patients with a known hypersensitivity to the active substance 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

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

VESOTA should be used with caution in patients with mild to moderate hepatic impairment (see sections 4.2, 4.3 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 VESOTA injection. Caution should be taken while administering VESOTA at the dorsogluteal injection site due to the proximity of the underlying sciatic nerve (see section 4.2).

VESOTA contains ethanol

VESOTA 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.

VESOTA contains benzyl alcohol

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

Paediatric population

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

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 estradiol, fulvestrant as in VESOTA may interfere with antibody-based estradiol assays and may result in falsely increased levels of estradiol.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

VESOTA is contraindicated in pregnancy (see section 4.3). VESOTA 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 VESOTA, 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 VESOTA. Fulvestrant as in VESOTA 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, the use of VESOTA during lactation is contraindicated (see section 4.3).

Fertility

The effect of VESOTA on fertility in humans has not been studied.

4.7. Effects on ability to drive and use machines

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

b. *Tabulated list of adverse reactions*

Table 1: Summary of adverse reactions for VESOTA

System organ class	Frequency	Adverse reaction
General disorders and administration site conditions	Frequent	Injection site reactions[a], asthenia, neuropathy peripheral[d], sciatica[d]
	Less frequent	Injection site haemorrhage[e], injection site haematoma[e], neuralgia[e]

Hepatobiliary disorders	Frequent	Elevated liver enzymes (ALT, AST, ALP)[b], elevated bilirubin[b]
	Less frequent	Elevated gamma-GT
	Frequency unknown	Hepatic failure, hepatitis
Gastrointestinal disorders	Frequent	Nausea, vomiting, diarrhoea
Immune system disorder	Frequent	Hypersensitivity reactions: angioedema and urticaria[d]
	Less frequent	Anaphylactic reactions
Musculoskeletal and connective tissue disorders	Frequent	Joint and musculoskeletal pain[c], back pain
Skin and subcutaneous tissue disorders	Frequent	Rash[d]
Vascular disorders	Frequent	Hot flushes[d], venous thromboembolism
Nervous system disorders	Frequent	Headache
Blood and lymphatic system	Frequent	Reduced platelet count[d]

Metabolism and nutrition disorders	Frequent	Anorexia
Infections and infestations	Frequent	Urinary tract infections
Reproductive system and breast disorders	Frequent	Vaginal haemorrhage[d]
	Less frequent	Vaginal moniliasis[e], leukorrea[e]

[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.

[e] ADR was not observed in the FALCON study that compared fulvestrant and anastrozole.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form', found under SAHPRA's publications:

https://www/sahpra.org.za/Publications/Index/8

4.9. Overdose

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 VESOTA. If overdose occurs, this should be managed symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological classification: A.21.12 Hormone inhibitors

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

Mechanism of action

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 estradiol.

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 L/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 14C-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*.

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 %).

Special Populations

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 preclinical 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 estradiol. 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
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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

VESOTA contains contain the following inactive ingredients:

Ethanol (96 %), benzyl alcohol, benzyl benzoate, castor oil.

6.2. Incompatibilities

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

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 5 °C.

Keep in original packaging until required for use.

6.5. Nature and contents of container

The pre-filled syringe presentation consists of a 5mL clear glass barrel with OVS tip cap and stoppered with grey plunger stopper along with transparent plunger rod. The PFS are packed in pre-printed carton with a packaging leaflet.

Pack size: 2 pre-filled syringes.

6.6. Special precautions for disposal and other handling

Instructions for administration:

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

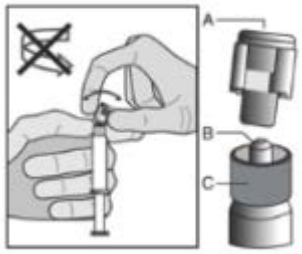
that it is not damaged.

• Peel open the safety needle (SafetyGlide) outer packaging.

• Parenteral solutions must be inspected visually for particulate matter and discolouration prior to administration.

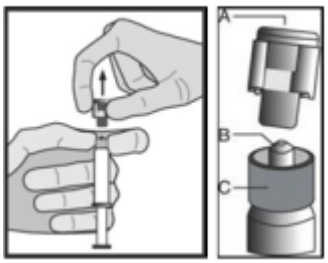
• Hold the syringe upright on the ribbed part (C). With the other hand, take hold of the cap (A) and carefully tilt back and forth until the cap disconnects and can be pulled off, do not twist (see Figure 1).

Figure 1



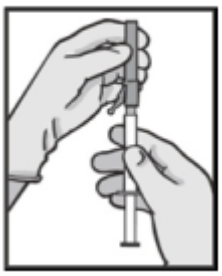
• Remove the cap (A) in a straight upward direction. To maintain sterility do not touch the syringe tip (B) (see Figure 2).

Figure 2



• Attach the safety needle to the 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.

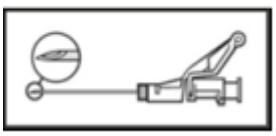
• Pull shield straight off needle to avoid damaging needle point.

• Transport filled syringe to point of administration.

• Remove needle sheath.

• Expel excess gas from the syringe.

Figure 4



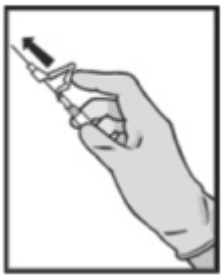
• Administer intramuscularly slowly (1-2 minutes/injection) into the buttock (gluteal area).

For user convenience, the needle bevel-up position is oriented to the lever arm (see Figure 4).

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

AUROGEN SA (Pty) Ltd

Woodhill Office Park, Building 1, First Floor

53 Phillip Engelbrecht Avenue

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Johannesburg

South Africa

8. Registration number

56/26/0406.405

9. Date of first authorisation

03 DECEMBER 2023