SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

FULVESTRANT MYLAN 250 mg (solution for injection)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effects

Contains 10 % 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 liquid, free from visible particulate matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

FULVESTRANT MYLAN 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

Special Population

Patients with renal insufficiency:

No dose adjustments are recommended for patients with 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, **FULVESTRANT MYLAN** 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 (see section 5.1).

Interactions requiring dose adjustments:

There are no known interactions requiring dose adjustment.

Method of Administration

It is recommended that the injection be administered slowly (1 – 2 minutes/injection). Caution should be taken if injecting **FULVESTRANT MYLAN** at the dorsogluteal site due to the proximity of the underlying sciatic nerve.

Refer to section 6.6 for detailed instructions on administration.

4.3 Contraindications

FULVESTRANT MYLAN is contraindicated in:

- patients with known hypersensitivity to fulvestrant or any of the excipients (see section 6.1).
- patients with severe hepatic impairment.
- pregnancy and breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

FULVESTRANT MYLAN should be used with caution in patients with mild to moderate hepatic impairment (see section 5.2 and 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 route of administration.

Thromboembolic events are observed in women with advanced breast cancer and have been observed in clinical trials with fulvestrant, as in **FULVESTRANT MYLAN**. This should be taken into consideration when prescribing **FULVESTRANT MYLAN** 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 Reactions

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

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

The efficacy and safety of fulvestrant have not been studied in patients with critical visceral disease.

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

FULVESTRANT MYLAN 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

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

Benzoate salt may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

Paediatric population

FULVESTRANT MYLAN 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 trial 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 (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Patients of childbearing potential should be advised to use effective contraception while on treatment and for two years after last dose.

Pregnancy

FULVESTRANT MYLAN 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 (see section 5.3). If pregnancy occurs while taking **FULVESTRANT MYLAN**, the patient must be informed of the potential hazard to the foetus and potential risk for loss of pregnancy.

Breast-feeding

Breast-feeding must be discontinued during treatment with **FULVESTRANT MYLAN**. 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 fulvestrant on fertility in humans have not been studied.

4.7 Effects on ability to drive and use machines

Fulvestrant has no or negligible influence on the ability to drive or use machines. However, since asthenia has been reported frequently 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

a) 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).

b) Tabulated list of adverse reactions

Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency groupings are defined as Frequent, Less frequent and Frequency unknown. Within each frequency grouping adverse reactions are reported in order of decreasing seriousness.

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, uticaria)
	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
Hepato-biliary disorders	*Frequent*	Elevated hepatic enzymes (ALT, AST, ALP) Elevated bilirubin
	Less frequent	Hepatic failure, hepatitis, elevated gamma-GT
Skin and subcutaneous tissue disorders	*Frequent*	Rash
Musculoskeletal and connective tissue disorders	*Frequent*	Joint and musculoskeletal pain (e.g. arthralgia, myalgia) Back pain
Reproductive system and breast disorders	*Frequent*	Vaginal haemorrhage
	Less frequent	Vaginal moniliasis, leukorrhea

MedDRA system organ class	Frequency	Adverse reactions
General disorders and administration site conditions	*Frequent*	Asthenia, injection site reactions Neuropathy peripheral, sciatica
	Less frequent	Injection site haemorrhage, injection site haematoma, neuralgia

c. Description of selected adverse reactions

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 this 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 on the SAHPRA website at: https://medsafety.sahpra.org.za/#download1, via email at: adr@sahpra.org.za or via telephone at: 0125010311

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.

If overdose occurs, this should be managed symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Fulvestrant is an anti-oestrogen. Its mode 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 an anti-oestrogen that 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*.

Effects 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 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 K167, a marker of tumour cell profileration.

Effects on the postmenopausal endometrium:

The pre-clinical data for fulvestrant suggests 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 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 MYLAN** 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

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 mg (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). (Ref 1)

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 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*.

Excretion:

Fulvestrant is cleared by the hepatobiliary route. Excretion is via the faeces and renal elimination of substance-related material was negligible (less than 1 %). Fulvestrant has a high clearance of 11 $\pm$ 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 population

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 2,4 - 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.

Paediatric Population

The pharmacokinetics of fulvestrant has been evaluated in a clinical study conducted in 30 girls, aged 1 to 8 years, with Progressive Precocious Puberty associated with McCune Albright Syndrome (see section 5.1). The patients received 4 mg/kg monthly intramuscular dose of fulvestrant. The geometric mean (standard deviation) steady state trough concentration (C_{min}, 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.

5.3 Preclinical safety data

The acute toxicity of fulvestrant is low.

Faslodex and other formulations of fulvestrant were well tolerated in animal species used in multiple dose studies. Local reactions, including myositis and granulomata at the injection site were attributed to the vehicle but the severity of myositis in rabbits increased with fulvestrant, compared to the saline control. In toxicity studies with multiple

intramuscular doses of fulvestrant in rats and dogs, the antioestrogenic activity of fulvestrant was responsible for most of the effects seen, particularly in the female reproductive system, but also in other organs sensitive to hormones in both sexes. Arteritis involving a range of different tissues was seen in some dogs after chronic (12 months) dosing.

In dog studies following oral and intravenous administration, effects on the cardiovascular system (slight elevations of the S-T segment of the ECG [oral], and sinus arrest in one dog [intravenous]) were seen. These occurred at exposure levels higher than in patients (C_{max} >15 times) and are likely to be of limited significance for human safety at the clinical dose.

Fulvestrant showed no genotoxic potential.

Fulvestrant showed effects upon reproduction and embryo/foetal development consistent with its antioestrogenic activity, at doses similar to the clinical dose. In rats, a reversible reduction in female fertility and embryonic survival, dystocia and an increased incidence of foetal abnormalities including tarsal flexure were observed. Rabbits given fulvestrant failed to maintain pregnancy. Increases in placental weight and post-implantation loss of foetuses were seen. There was an increased incidence of foetal variations in rabbits (backwards displacement of the pelvic girdle and 27 pre-sacral vertebrae).

A two-year oncogenicity study in rats (intramuscular administration of Faslodex) showed increased incidence of ovarian benign granulosa cell tumours in female rats at the high dose, 10 mg/rat/15 days and an increased incidence of testicular Leydig cell tumours in males. In a two-year mouse oncogenicity study (daily oral administration) there was an

increased incidence of ovarian sex cord stromal tumours (both benign and malignant) at doses of 150 and 500 mg/kg/day. At the no-effect level for these findings, systemic exposure levels (AUC) were, in rats, approximately 1,5-fold the expected human exposure levels in females and 0.8-fold in males, and in mice, approximately 0,8-fold the expected human exposure levels in both males and females. Induction of such tumours is consistent with pharmacology-related endocrine feedback alterations in gonadotropin levels caused by antioestrogens in cycling animals. Therefore, these findings are not considered to be relevant to the use of fulvestrant in postmenopausal women with advanced breast cancer.

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

24 months

6.4 Special precautions for storage

Store between 2 °C to 8 °C (in a refrigerator).

Do not freeze.

Store in the original package.

6.5 Nature and contents of container

The pre-filled syringe presentation consists of 2 x 5 ml clear neutral glass (Type 1) barrels, each containing a nominal 5 ml of **FULVESTRANT MYLAN** solution for injection and fitted with a tamper evident closure.

The syringes are presented in a tray with polystyrene plunger rod and 2 safety needles (SafetyGlide™) for connection to each barrel.

6.6 Special precautions for disposal and other handling

See section 4.2

NOTE: Due to the proximity of the underlying sciatic nerve, caution should be taken if administering **FULVESTRANT MYLAN** 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 single-dose prefilled syringe:

1) Remove glass syringe barrel from tray and check that it is not damaged.
2) Remove perforated patient record label from syringe.
3) Parenteral solutions must be inspected visually for particulate matter and discolouration prior to administration. Discard if particulate matter or discoloration is present.
4) Peel open the safety needle (SafetyGlide™) outer packaging.

5) 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 (DO NOT TWIST CAP) until the cap disconnects for removal (see Figure 1).

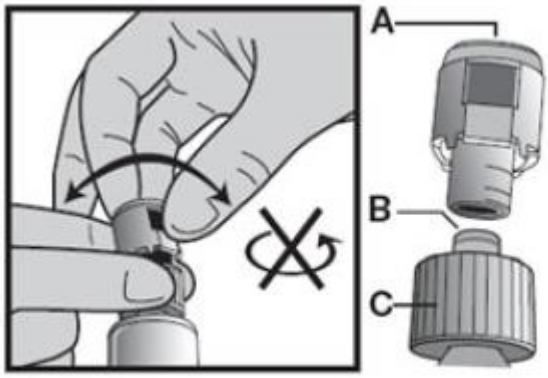

Figure 1

6) Pull the cap (A) off in a straight upward direction. DO NOT TOUCH THE STERILE SYRINGE TIP (Luer-Lok) (B) (see Figure 2).

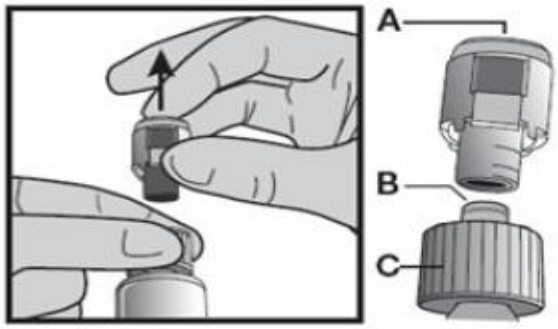

Figure 2

7) Attach the safety needle to the syringe tip Luer-Lok.

Twist needle until firmly seated (see Figure 3). Confirm that the needle is locked to the Luer connector before moving or tilting the syringe out of the vertical plane to avoid spillage of syringe contents.

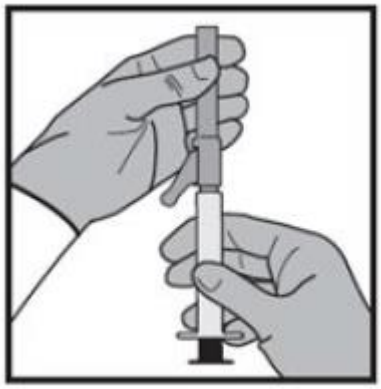

Figure 3

For Administration:

8) Pull shield straight off needle to avoid damaging needle point.
9) Remove needle sheath.
10) Expel excess gas from the syringe (a small gas bubble may remain).
11) 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).

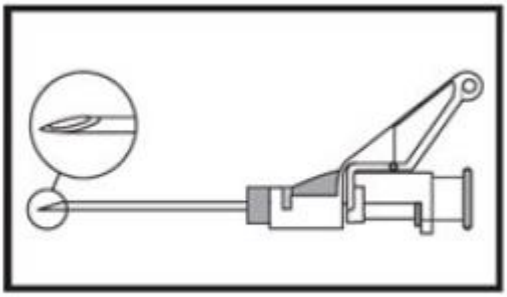

Figure 4

12) After injection, immediately activate the lever arm to deploy the needle shielding by applying a single-finger stroke to the activation assisted lever arm to push the lever arm completely forward. Listen for a click. Confirm that the needle shielding has completely covered the needle (see Figure 5). NOTE: Activate away from self and others.

Figure 5

13) Discard the empty syringe into an approved sharps collector in accordance with applicable regulations and institutional policy (see '*Disposal*').
14) Repeat steps 1 through 13 for second syringe.

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

Mylan (Pty) Ltd

Building 6, Greenstone Hill Office Park

Emerald Boulevard

Modderfontein, 1645

Republic of South Africa

8 REGISTRATION NUMBER

50/21.12/1066

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03 November 2020

10 DATE OF REVISION OF THE TEXT

03 July 2024