PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

FASTELEV 250 mg/5 ml solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

One pre-filled syringe contains 250 mg/5 ml fulvestrant. Each ml contains 50 mg fulvestrant.

Excipients with known effect:

Each pre-filled syringe contains:

Benzyl alcohol, benzyl benzoate, 10 % m/v ethanol 96 %.

For the full list of excipients, refer to **section 6.1.**

3. PHARMACEUTICAL FORM:

Solution for injection in pre-filled syringe.

A clear, colourless to yellow viscous solution. Parenteral solutions must be inspected visually for particulate matter and discolouration prior to administration.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

FASTELEV is indicated for the treatment of postmenopausal women with oestrogen receptor positive, locally advanced or metastatic breast cancer for 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:

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

Adults females (including the elderly):

The recommended dose is 500 mg to be administered intramuscularly as two 5 ml injections, one in each buttock, 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 to 2 minutes/injection).
For detailed instruction for administration (**see section 6.6**).

Children:

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

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, **FASTELEV** 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.

Interactions requiring dose adjustments:

There are no known medicine interactions requiring dose adjustment.

4.3 Contraindications:

FASTELEV is contraindicated in:

- Patients with a known hypersensitivity to fulvestrant or to any of the ingredients of **FASTELEV.**
- Patients with severe hepatic impairment (see **section 4.4).**
- Pregnancy and lactation (see **section 4.6**).

4.4 Special warnings and precautions for use:

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

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

Caution should be used before treating patients with bleeding diatheses or thrombocytopenia or patients on anticoagulants due to the intramuscular route of administration (see **section 4.8**).

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

Hypersensitivity reactions such as angioedema and urticaria have been frequently reported and may be serious (see **section 4.8**).

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

There is no long term data on the effect of **FASTELEV** on bone. Due to the mechanism of action of **FASTELEV**, there is a potential risk of osteoporosis.

The efficacy and safety of PN have not been studied in patient with critical visceral diseases.

Interference with 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.

Paediatric population:

FASTELEV is not recommended for use in children and adolescents as safety and efficacy have not been established.

FASTELEV contains ethanol 96 % (alcohol):

FASTELEV contains ethanol (alcohol), i.e. up to 1000 mg per dose, equivalent to 20 ml beer or 8 ml of wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breastfeeding women, children and high risk groups such as patients with liver disease, or epilepsy.

FASTELEV contains benzyl alcohol:

FASTELEV contains benzyl alcohol, which may cause allergic/anaphylactoid reactions.

4.5 Interaction with other medicines and other forms of interaction:

It has been reported that 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 **FASTELEV** and CYP3A4 inhibitors or inducers concomitantly.

4.6 Fertility, pregnancy and lactation:

Women of child bearing potential / Contraception in males and females:

Patients of child bearing potential should be advised to use effective contraception while on treatment.

Pregnancy:

FASTELEV 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 **FASTELEV**, 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 **FASTELEV**. 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 breastfed infants, use during lactation is contraindicated (see **section 4.3**).

Fertility:

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

4.7 Effects on ability to drive and use machines:

During treatment with **FASTELEV,** asthenia has been reported frequently and caution should be observed by those patients who experience this symptom when driving or operating machinery.

4.8 Undesirable effects:

Summary of the safety profile:

The most frequently reported side effects are injection site reactions, asthenia, nausea, and increased hepatic enzymes (ALT, AST, ALP).

Adverse Drug Reactions reported in patients treated with fulvestrant monotherapy:

Adverse reactions by system organ class and frequency		
Infections and infestations:	*Frequent*	Urinary tract infections, pharyngitis.
Blood and the lymphatic system disorders:	*Less frequent*	Reduced platelet count[e].
Immune system disorders:	*Frequent*	Hypersensitivity reactions[e]. Angioedema, urticaria.
	Less frequent	Anaphylactic reactions.
Metabolism and nutrition disorders:	*Frequent*	Anorexia[a].
Nervous system disorders:	*Frequent*	Headache.
Vascular disorders:	*Frequent*	Venous thromboembolism[a], hot flushes[e].

Gastrointestinal disorders:	*Frequent*	Nausea, vomiting and diarrhoea.
Hepato-biliary disorders:	*Frequent*	Increased hepatic enzymes (ALT, AST, ALP) [a], elevated bilirubin[a].
	Less frequent	Hepatic failure[c,f], hepatitis[f], elevated gamma-GT[f].
Skin and subcutaneous tissue disorders:	*Frequent*	Rash[e].
Musculoskeletal, connective tissue and bone disorders:	*Frequent*	Back pain[a], joint and musculoskeletal pain[d].
Reproductive system and breast disorders:	*Less frequent*	Vaginal moniliasis[f], leukorrhoea[f], vaginal haemorrhage[e].
General disorders and administrative site conditions:	*Frequent*	Asthenia[a], injection site reactions[b], sciatica[e], peripheral neuropathy[e].
	Less frequent	Injection site haemorrhage[f], injection site haematoma[f], neuralgia[c,f] .

[a] Includes adverse medicine reactions for which the exact contribution of **FASTELEV** cannot be assessed due to the underlying disease.

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

[c] The event was not observed in major clinical studies. The frequency has been calculated using the upper limit of the 95 % confidence interval for the point estimate. This is calculated as 3/560 (where 560 is the number of patients in the major clinical studies), which equates to a frequency category of 'less frequent'.

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

[e] Frequency category differs between pooled safety dataset and clinical study.

[f] ADR was not observed in clinical study.

4.9 Overdose:

There is no human experience of overdose. Animal studies suggest that no effects other than those related directly or indirectly to anti-oestrogenic activity were evident with higher doses of **FASTELEV**. If overdose occurs, symptomatic supportive treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

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

Mechanism of action and pharmacodynamic effects:

Fulvestrant is a competitive oestrogen receptor (ER) antagonist with an affinity comparable to estradiol. The mechanism of action is associated with downregulation of oestrogen receptor protein levels and can be described as an oestrogen receptor downregulator (ER downregulator). 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 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:

Absorption:

After administration of fulvestrant long acting intramuscular injection, fulvestrant is slowly absorbed and maximum plasma concentrations (Cmax) 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, Cmax 25,1 [35,3 %] ng/ml, Cmin 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 distribution at steady state (Vd_{ss}) 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 but 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-gluscuronide 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 metabolised form. 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 ($t_{½}$) after intramuscular administration is governed by the absorption rate and was estimated to be 50 days.

Special populations:

Reports have shown that in a population pharmacokinetic analysis of data from Phase 3 studies, no difference in fulvestrant's pharmacokinetic profile was detected with regard to age (range 33 to 89 years), weight (40 to 127 kg).

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.

Environmental Risk Assessment (ERA):

Environmental risk assessment studies have shown that fulvestrant may have potential to cause adverse effects to the aquatic environment (see **section 4.4**).

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Benzyl alcohol

Benzyl benzoate

Castor oil, refined

Ethanol (96 %)

6.2 Incompatibilities:

In the absence of compatibility studies, **FASTELEV** must not be mixed with other medicines.

6.3 Shelf life:

2 years.

6.4 Special precautions for storage:

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

Do not freeze.

Store in the original package. Protect from light.

6.5 Nature and contents of container:

FASTELEV pre-filled syringe consists of the following:

- 5 ml Type I, borosilicate syringe barrel with cut flange (CF) and Luer lock adapter (LA).

- Plastic Rigid Tip Cap (PRTC) consisting of a rigid polypropylene shell and elastomeric tip cap.
- The 5 ml pre-filled syringe is aseptically sealed with a grey bromobutyl plunger stopper.
- Clear polypropylene backstop.
- Sterile disposable needle (21 G x 1½ TW) separately packed in secondary packaging.

Two (2) x 5 ml pre-filled syringes are packed in an outer cardboard carton.

6.6 Special precautions for disposal and other handling:

Method of administration:

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 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 (refer to **Figure 1**).

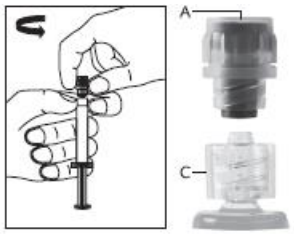


Figure 1

Twist to lock the needle to the Luer connector.

Peel open the safety needle outer packaging.

Attach the safety needle to the Luer-Lok (refer to **Figure 2**).

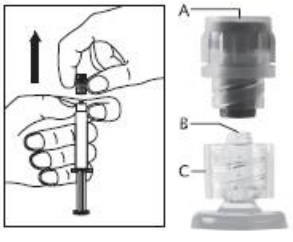


Figure 2

Twist until firmly seated.

Pull shield straight off needle to avoid damaging needle point (refer to **Figure 3**).

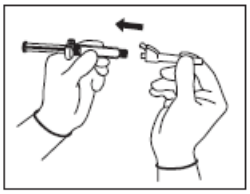


Figure 3

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 to 2 minutes/injection) into the buttock. For user convenience, the needle bevel-up position is oriented to the lever arm (refer to **Figure 4**).

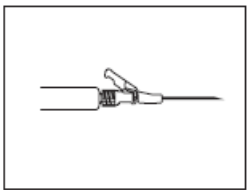


Figure 4

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

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

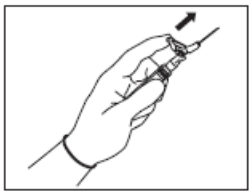


Figure 5

Disposal:

Pre-filled syringes are for single use only.

FASTELEV may pose a risk to the aquatic environment. Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park, Magwa Crescent West

Waterfall City

Midrand

Gauteng

2090

8. REGISTRATION NUMBER(S):

52/21.12/0472

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

3 March 2020

10. DATE OF REVISION OF THE TEXT:

3 March 2020