FULVESTRANT FRESENIUS KABI 250 MG/5ML
SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe of 5 ml contains 250 mg fulvestrant.

Excipients with known effect (per 5 ml)
Ethanol 96% (alcohol), 500 mg
Benzyl alcohol (E1519), 500 mg
Benzyl benzoate, 750 mg

For the full list of excipients, see List of excipients.

PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe
Clear, colorless to yellow, viscous solution, free from visible particles.

THERAPEUTIC INDICATIONS

Fulvestrant is indicated:

- as monotherapy for the treatment of estrogen receptor positive, locally advanced or metastatic breast cancer in postmenopausal women:
    - who are human epidermal growth factor receptor 2 (HER2)-negative and not previously treated with endocrine therapy, or
    - with disease relapse on or after adjuvant t endocrine herapy, or disease progression on endocrine therapy.
- in combination with ribociclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in postmenopausal women, as initial endocrine based therapy or following disease progression on endocrine therapy*.
- in combination with abemaciclib for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy*.
- in combination with palbociclib for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in women who have received prior endocrine therapy* (see Pharmacodynamic Properties).

In pre- or perimenopausal women, the combination treatment with palbociclib or abemaciclib should be combined with a luteinizing hormone releasing hormone (LHRH) agonist.

** This indication only applicable in markets where palbociclib, ribociclib or abemaciclib are registered.*

POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Adult females (including elderly)
The recommended dose is 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose.

When fulvestrant is used in combination with palbociclib, abemaciclib or ribociclib, please also refer to the Summary of Product Characteristics of palbociclib, abemaciclib or ribociclib.

Prior to the start of treatment with the combination of fulvestrant plus palbociclib, or abemaciclib, and throughout its duration, pre/perimenopausal women should be treated with LHRH agonists according to local clinical practice.

Special populations

Paediatric patient
The safety and efficacy of fulvestrant in children from birth to 18 years of age have not been established. Currently available data are described in sections Pharmacodynamic Properties and Pharmacokinetic Properties, but no recommendation on a posology can be made.

Renal impairment
No dose adjustments are recommended for patients with mild to moderate renal impairment (creatinine clearance ≥ 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 Special Warnings and Precautions for Use).

Hepatic impairment
No dose adjustments are recommended for patients with mild to moderate hepatic impairment. However, as fulvestrant exposure may be increased, fulvestrant should be used with caution in these patients. There are no data in patients with severe hepatic impairment (see sections Contraindications, Special Warnings and Precautions for Use and Pharmacokinetic Properties).

Method of administration
Fulvestrant 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 fulvestrant at the dorsogluteal site due to the proximity of the underlying sciatic nerve.

For detailed instructions for administration, see Instructions for administration and Special precautions for disposal.

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients listed.
Pregnancy and lactation (see Pregnancy and lactation)
Severe hepatic impairment (see Special Warnings and Precautions for Use and Pharmacokinetic Properties).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Fulvestrant should be used with caution in patients with mild to moderate hepatic impairment (see Posology and Method of administration, Contraindications, and Pharmacokinetic Properties).

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

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

Thromboembolic events are commonly observed in women with advanced breast cancer and have been observed in clinical trials with fulvestrant (see Undesirable Effects). This should be taken into consideration when prescribing fulvestrant 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 fulvestrant at the dorsogluteal injection site due to the proximity of the underlying sciatic nerve (see Posology and Method of Administration and Undesirable Effects).

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

When fulvestrant is combined with palbociclib, please also refer to the Summary of Product Characteristics of palbociclib.

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.

Ethanol
This medicinal product contains 500 mg of alcohol (ethanol) in each injection which is equivalent to 100 mg/ ml (10% w/v). The amount in each injection of this medicine is equivalent to 13 ml beer or 5 ml wine.

A dose of 500 mg of this medicine (both syringes) administered to an adult women weighing 70 kg would result in exposure to 14.3 mg / kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 2.4 mg /100 ml (see Appendix I of report EMA/CHMP/43486/2018).
For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be about 50 mg/ 100 ml.

Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects.

Benzyl alcohol
This medicinal product contains benzyl alcohol as an excipient which may cause allergic reactions.

Paediatric population
Fulvestrant is not recommended for use in children and adolescents as safety and efficacy have not been established in this group of patients (see Pharmacodynamic Properties).

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.

FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential

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

Pregnancy

Fulvestrant is contraindicated in pregnancy (see Contraindications). 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 fulvestrant, 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. 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 Contraindications).

Fertility

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

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 very commonly with fulvestrant, caution should be observed by those patients who experience this adverse reaction when driving or operating machinery.

UNDESIRABLE EFFECTS

Tabulated list of adverse reactions

Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency groupings are defined according to the following convention: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100). Within each frequency grouping adverse reactions are reported in order of decreasing seriousness.

Table 1 Adverse Drug Reactions reported in patients treated with fulvestrant monotherapy

Adverse reactions by system organ class and frequency		
Infections and infestations	Common	Urinary tract infections
Blood and lymphatic system disorders	Common	Reduced platelet count[e]
Immune system disorders	Very common	Hypersensitivity reactions[e]
	Uncommon	Anaphylactic reactions
Metabolism and nutrition disorders	Common	Anorexia[a]
Nervous system disorders	Common	Headache
Vascular disorders	Very common	Hot flushes[e]
	Common	Venous thromboembolism[a]
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting, diarrhoea
Hepatobiliary disorders	Very common	Elevated hepatic enzymes (ALT, AST, ALP)[a]
	Common	Elevated bilirubin[a]
	Uncommon	Hepatic failure[c,f], hepatitis[f], elevated gamma-GT[f]
Skin and subcutaneous tissue disorders	Very common	Rash[e]
Musculoskeletal and connective tissue	Very common	Joint and musculoskeletal pain[d]

disorders	Common	Back pain[a]
Reproductive system and breast disorders	Common	Vaginal haemorrhage[e]
	Uncommon	Vaginal moniliasis[f], leukorrhea[f]
General disorders and administration site conditions	Very common	Asthenia[a], injection site reactions[b]
	Common	Neuropathy peripheral[e], sciatica[e]
	Uncommon	Injection site haemorrhage[f], injection site haematoma[f], neuralgia[c,f]

a. Includes adverse drug reactions for which the exact contribution of fulvestrant cannot be assessed due to the underlying disease.
b. The term injection site reactions does not include the terms injection site haemorrhage and injection site haematoma, sciatica, neuralgia and neuropathy peripheral.
c. The event was not observed in major clinical studies.
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.

OVERDOSE

There are isolated reports of overdose with fulvestrant in humans. If overdose occurs, symptomatic supportive treatment is recommended. Animal studies suggest that no effects other than those related directly or indirectly to anti-estrogenic activity were evident with higher doses of fulvestrant.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Endocrine therapy, Anti-estrogens, ATC code: L02BA03

Mechanism of action and pharmacodynamic effects

Fulvestrant is a competitive estrogen receptor (ER) antagonist with an affinity comparable to estradiol.

Fulvestrant blocks the trophic actions of estrogens without any partial agonist (estrogen-like) activity. The mechanism of action is associated with down-regulation of estrogen receptor protein levels.

Clinical trials 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 estrogen 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.

Effects on bone

There are no long-term data on the effect of fulvestrant on bone. Neoadjuvant treatment for up to 16 weeks in breast cancer patients with either fulvestrant 500 mg or fulvestrant 250 mg did not result in clinically significant changes in serum bone-turnover markers.

Paediatric population

Fulvestrant is not indicated for use in children.

Pharmacokinetic properties

Absorption

After administration of fulvestrant long-acting intramuscular injection, fulvestrant 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 500mg.

Distribution

Fulvestrant is subject to extensive and rapid distribution. The large apparent volume of 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 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-estrogen 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 ($t_{1/2}$) 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 3 studies, no difference in fulvestrant's pharmacokinetic profile was detected with regard to age (range 33 to 89 years), weight (40-127 kg) or race.

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 trial conducted in subjects 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.

Paediatric population

The pharmacokinetics of fulvestrant has been evaluated in a clinical trial conducted in 30 girls. Although the data collected were limited, the steady-state trough concentrations of fulvestrant in children appear to be consistent with those in adults.

PHARMACEUTICAL PARTICULARS

List of excipients
Ethanol (96%)
Benzyl alcohol (E1519)
Benzyl benzoate
Castor oil, refined

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

Shelf life
2 years.

Special precautions for storage
Store below 30°C.
Store the pre-filled syringe in the original package in order to protect from light.

Nature and contents of container
The pre-filled syringe presentation consists of:
Two clear glass pre-filled syringes with plunger rod and plunger stopper, fitted with a Plastic Rigid Tip cap, each containing 5 ml fulvestrant solution for injection. Two safety needles (BD SafetyGlide) for connection to each barrel are also provided.

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 fulvestrant at the dorsogluteal injection site (see Special warnings and precautions for use).

Warning - Do not autoclave safety needle (BD SafetyGlide) 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 twist the plastic rigid tip cap in anticlockwise direction. (see Figure 1):

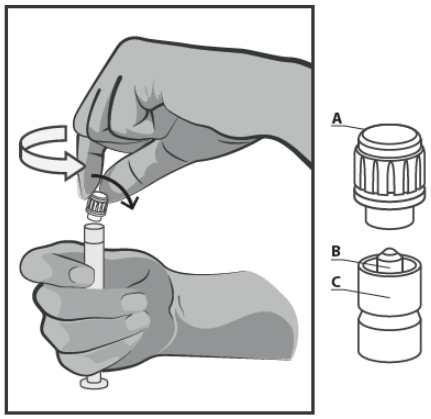

Figure 1

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

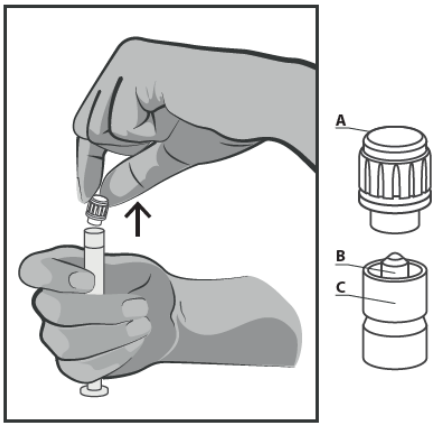

Figure 2

- Attach the safety needle to the Luer-Lok and twist until firmly seated (see Figure 3).
- 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.

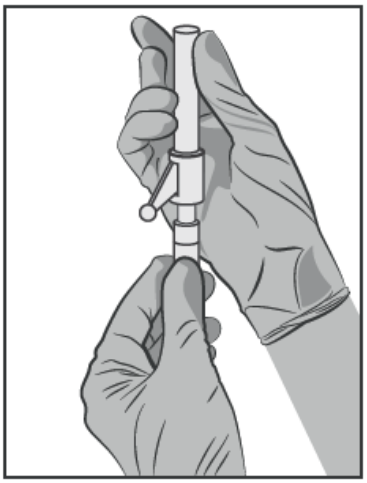

Figure 3

- 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).

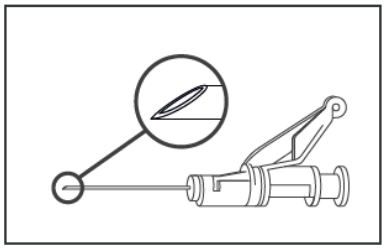

Figure 4

- 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.

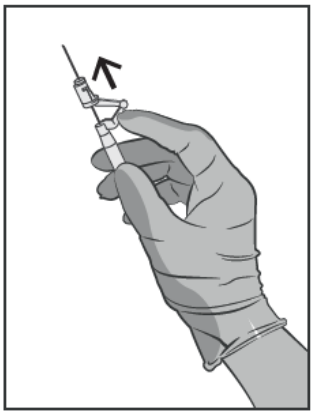

Figure 5

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.

MANUFACTURER
Laboratorios Farmalan, S.A.,
C/ La Vallina, s/n, Polígono Industrial Navatejera,
Villaquilambre,
24193 León, Spain.

PRODUCT REGISTRATION HOLDER / IMPORTER
Fresenius Kabi Malaysia Sdn Bhd
3-1& 3-2, Axis Technology Centre,
Lot 13, Jalan 51A/225,
46100 Petaling Jaya,
Selangor, Malaysia.

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