KEMFLUD
FULVESTRANT 250 mg / 5 ml

SOLUTION FOR INJECTION FOR INTRAMUSCULAR USE

Argentine Industry **Prescription drug only**

QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each vial of KEMFLUD contains:

Fulvestrant	250.0 mg
Ethanol 96 %	500.0 mg
Benzyl alcohol	500.0 mg
Benzyl benzoate	750.0 mg
Castor oil q.s.f.	5.0 ml

MECHANISM OF ACTION
Endocrine therapy, antiestrogen
ATC Code: L02BA03

INDICATIONS
KEMFLUD is indicated for the treatment of estrogen receptor positive, locally advanced or metastatic breast cancer in postmenopausal women, with disease relapse on or after adjuvant antiestrogen therapy, or disease progression on

PHARMACEUTICAL FORM / PROPERTIES

Pharmaceutical action
Fulvestrant is a competitive estrogen receptor (ER) antagonist with an affinity comparable to estradiol. Fulvestrant blocks the trophic actions of estrogens without partial agonist (estrogen-like) activity. The mechanism of action is associated with downregulation of estrogen receptor (ER) protein levels. Clinical studies in postmenopausal women with primary breast cancer have shown that Fulvestrant significantly downregulates ER protein in ER positive tumors 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 tumors in postmenopausal neoadjuvant setting.

Clinical efficacy and safety in advanced breast cancer
A Phase 2 clinical study was completed in 736 postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. The study included 423 patients whose disease had recurred or progressed during antiestrogen therapy (AE subgroup) and 313 patients whose disease had recurred or progressed during aromatase inhibitor therapy (AI subgroup). This study compared the efficacy and 9 safety of Fulvestrant 500 mg (n=362) with Fulvestrant 250 mg (n=374). Progression-free survival (PFS) was the primary endpoint; key secondary efficacy endpoints included objective response rate (ORR), clinical benefit rate (CBR) and overall survival (OS). Efficacy results for the CONFIRM study are summarized in Table 1.

Table 1 Summary of results of the primary efficacy endpoint (PFS) and key secondary efficacy endpoints in the CONFIRM

Variable	Type of estimate; Treatment Comparison	Fulvestrant 500 mg (N=362)	Fulvestrant 250 mg (N=374)	Comparison between groups (Fulvestrant 500 mg/Fulvestrant 250 mg) "Hazard ratio"	95% CI	p-value
PFS	K-M median; in months: hazard ratio					
All patients		6.5	5.5	0.80	0.68, 0.94	0.006
-AE subgroup (n=423)		8.6	5.8	0.76	0.62, 0.94	0.013
- AI subgroup (n=313)[a]		5.4	4.1	0.85	0.67, 1.08	0.195
OS	K-M median; in months: hazard ratio					
All patients		25.1	22.8	0.84	0.69, 1.03	0.091
-AE subgroup (n=296)		27.9	25.9	0.85	0.65, 1.13	0.264
-AI subgroup (n=205)[a]		24.1	20.8	0.83	0.62, 1.12	0.216

Variable	Type of estimate; Treatment Comparison	Fulvestrant 500 mg (N=362)	Fulvestrant 250 mg (N=374)	Comparison between groups (Fulvestrant 500 mg/Fulvestrant 250 mg) Absolute difference in %	95% CI
ORR[d]	% of patients with CB; absolute difference in %				
All patients		13.8	14.6	-0.8	-5.8; 6.3
- AE subgroup (n=423)		18.1	19.1	-1.0	-8.2; 9.3
- AI subgroup (n=313)a		7.3	8.3	-1.0	-5.5; 9.8
CBR[e]	% of patients with BC; absolute difference in %				
All patients		45.6	39.6	6.0	-1.1; 13.3
- AE subgroup (n=423)		52.4	45.1	7.3	-2.2; 16.6
- AI subgroup (n=313)[a]		36.2	32.3	3.9	-6.1; 15.2

Fulvestrant is indicated in patients whose disease had recurred or progressed on an antiestrogen therapy. The results in the AI subgroup are inconclusive

Two Phase 3 clinical studies were completed in a total of 851 postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. Seventy seven percent (77%) of the study population had estrogen receptor positive breast cancer. These studies compared the safety and efficacy of monthly administration of Fulvestrant 250 mg versus the daily administration of 1 mg anastrozole (aromatase inhibitor). Overall, Fulvestrant at the 250 mg monthly dose was at least as effective as anastrozole in terms of progression-free survival, objective response, and time to death. There were no statistically significant differences in any of these endpoints between the two treatment groups. Progression-free survival was the primary endpoint. Combined analysis of both studies showed that 83% of patients who received Fulvestrant progressed, compared with 85% of patients who received anastrozole. Combined analysis of both studies showed the hazard ratio of Fulvestrant 250 mg to anastrozole for progression-free survival was 0.95 (95% CI 0.82 to 1.10). The objective response rate for Fulvestrant 250 mg was 19.2% compared with 16.5% for anastrozole. The median time to death was 27.4 months for patients treated with Fulvestrant and 27.6 months for patients treated with anastrozole. The hazard ratio of Fulvestrant 250 mg to anastrozole for time to death was 1.01 (95% CI 0.86 to 1.19).

Effects on the postmenopausal endometrium:
Preclinical data do not suggest a stimulatory effect of Fulvestrant on the postmenopausal endometrium. A 2-week study in healthy postmenopausal volunteers treated with 20 µg per day of ethinylestradiol showed that pre-treatment with Fulvestrant 250 mg resulted in significantly reduced stimulation of the postmenopausal endometrium, compared to pre-treatment with placebo, as judged by ultrasound measurement of endometrium thickness.
Neoadjuvant treatment for up to 16 weeks in breast cancer patients treated with either Fulvestrant 500 mg or Fulvestrant 250 mg did not result in clinically significant changes in endometrial thickness, indicating a lack of agonist effect. There is no evidence of adverse endometrial effects in the breast cancer patients studied. No data are available regarding endometrial morphology. In two short-term studies (1 and 12 weeks) in premenopausal patients with benign gynecologic disease, no significant differences in endometrial thickness were observed by ultrasound measurement between Fulvestrant and placebo groups.

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.

Pediatric Population
Fulvestrant is not indicated for use in children.
An open-label Phase 2 study investigated the safety, efficacy and pharmacokinetics of fulvestrant in 30 girls aged 1 to 8 years with Progressive Precocious Puberty associated with McCune Albright Syndrome (MAS). The pediatric patients received 4 mg/kg monthly intramuscular dose of Fulvestrant. This 12-month study investigated a range of MAS endpoints and showed a reduction in the frequency of vaginal bleeding and a reduction in the rate of bone age advancement. The steady state through concentrations of Fulvestrant in children in this study were consistent with that in adults. There were no new safety concerns arising from this small study, but 5-year data are yet not available.

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 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.

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-glucuronide metabolites) are either less active or 17 exhibit similar activity to Fulvestrant in antiestrogen 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 metabolized form. The major route of excretion is via the feces, 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
In a population pharmacokinetic analysis of data from Phase 3 studies, no difference in Fulvestrant's pharmacokinetic profile was detected regarding 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 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.

Pediatric 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 pediatric patients were aged 1 to 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.

DOSAGE/STRENGTHS
The recommended dose is 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose

ADMINISTRATION

Instructions for administration
Fulvestrant should be administered slowly (1-2 minutes / injection) by two consecutive intramuscular injections of 250 mg / 5 ml, one in each buttock.

Instructions for Administration
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.
- Use a syringe with its respective needle to withdraw the contents of a vial.
- Remove the needle that was used and insert a new one.
- Parenteral solutions should be visually inspected for particulate content and discoloration prior to administration,
- Take the filled syringe to the site of administration.
- Remove the cap from the needle.
- Remove excess gas from the syringe.
- Insert the intramuscular needle into the appropriate gluteal area.
- Administer slowly by this route (1-2 minutes / injection). For greater comfort, the needle position with the bevel up.

Disposal
The vial, needles and syringes are for single use only.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

CONTRAINDICATIONS
Fulvestrant is contraindicated in patients with:
- A known hypersensitivity to the drug or to any of its components.
- Pregnancy and breast-feeding.
- Severe hepatic impairment.

WARNINGS
Fulvestrant should be used with caution in patients with mild to moderate hepatic impairment.
Fulvestrant x 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, Thromboembolic events are commonly observed in women with advanced breast cancer and have been observed in clinical studies with Fulvestrant. This should be taken into consideration when prescribing Fulvestrant 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.

Pediatric Population
Fulvestrant is not recommended for use in children and adolescents as safety and efficacy have not been established in this group of patients.

PRECAUTIONS

Interactions due to the use of other substances / medications
A clinical interaction study with Midazolam (CYP3A4 substrate) demonstrated that Fulvestrant does not inhibit CYP3A4.
Clinical interaction studies with Rifampicine (CYP3A4 inducer) and Ketoconazol (CYP3A4 inhibitor) 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.

Carcinogenesis, mutagenesis, and fertility disorders
The acute toxicity of Fulvestrant is low.
Fulvestrant formulations were well tolerated in animal species used in multiple does 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 antiestrogenic 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 (Cmax >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/fetal development consistent with its antiestrogenic 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 fetal abnormalities including tarsal flexure were observed. Rabbits given Fulvestrant failed to maintain pregnancy. Increases in placental weight and post-implantation loss of fetuses were seen. There was an increased incidence of fetal variations in rabbits (backwards displacement of the pelvic girdle and 27 pre-sacral vertebrae). A two-year oncogenicity study in rats (intramuscular administration of Fulvestrant) showed increased incidence of ovarian benign granulosa cell tumors in female rats at the high dose, 10 mg/rat/15 days and an increased incidence of testicular Leydig cell tumors in males. In a two-year mouse oncogenicity study (daily oral administration) there was an increased incidence of ovarian sex cord stromal tumors (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 tumors is consistent with pharmacology-related endocrine feedback alterations in gonadotropin levels caused by antiestrogens in cycling animals. Therefore, these findings are not considered to be relevant to the use of Fulvestrant in postmenopausal women with advanced breast cancer.

Fertility, pregnancy and breast-feeding
Women of childbearing potential: Patients of childbearing potential should use effective contraception during treatment with Fulvestrant.
Pregnancy: Fulvestrant is contraindicated in pregnancy.
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 fetal abnormalities and deaths. If pregnancy occurs while taking Fulvestrant, the patient must be informed of the potential hazard to the fetus and potential risk for loss of pregnancy.
Breast-feeding: 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 breast-feeding is contraindicated.
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 KEMFLUD, caution should be observed by those patients who experience this adverse reaction when driving or operating machinery.

Use in Pediatric population
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 Pharmacological Properties, but no recommendation on a dosage can be made.

Use in Elderly population
Adult females (including elderly): The recommended dose is 500 mg at intervals of one month, with an additional 500 mg dose administered two weeks after the initial dose.

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).

Hepatic impairment
No dose adjustments are recommended for patients with mild to moderate hepatic impairment. However, as Fulvestrant exposure may be increased, KEMFLUD should be used with caution in these patients. There are no data in patients with severe hepatic impairment.

Efecto sobre la capacidad para conducir y utilizar máquina
KEMFLUD has negligible influence on the ability to drive or use machines. However, since asthenia has been reported during treatment with KEMFLUD, caution should be observed by those patients who experience this symptom when driving or operating machines.

ADVERSE REACTIONS / SIDE EFFECTS
The most frequently reported adverse reactions are injection site reactions, asthenia, nausea, and elevated liver enzymes (ALT, AST, ALP).
the following frequency categories for adverse drug reactions (ADRs) were calculated based on Fulvestrant treatment group in pooled safety analyses of CONFIRM (Study D6997C00002), FINDER 1 (Studio D6997C00004), FINDER 2 (Study D6997C00006) and NEWEST (Study D6997C00003) studies that compared Fulvestrant 500 mg with Fulvestrant 250 mg. The frequencies in the following table are based on all reported adverse drug reactions, regardless of the investigator assessment of causality.
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).

Adverse reactions by system organ class and frequency		
Infections and infestations	Common	Urinary tract infection
Immune system disorders	Very common	Hypersensitivity reactions
Metabolism and nutrition disorders	Common	Anorexia
Nervous system disorders	Common	Headache
Vascular disorders	Very common	Venous thromboembolism, hot flushes
Gastrointestinal disorders	Very common	Nauseas
	Common	Vomiting, diarrhea
Hepatobiliary disorders	Very common	Elevated hepatic enzymes (ALT, AST, ALP)
	Common	Elevated bilirubin
	Uncommon	Hepatic failure, hepatitis, elevated gamma-GT
Skin and subcutaneous tissue disorders	Common	Rash
Musculoskeletal and connective tissue disorders	Common	Back pain
Reproductive system and breast disorders	Uncommon	Vaginal moniliasis, leukorrhea
General disorders and administration site	Very common	Asthenia, injection site reactions
	Uncommon	Injection site hemorrhage, injection site hematoma, neuralgia

OVERDOSE
There is no experience of overdose in humans. Animal studies suggest that no effects other than those directly or indirectly related to antiestrogenic activity were shown at higher doses of Fulvestrant. In case of overdose, supportive symptomatic treatment is recommended.

In the event of an overdose, go to the nearest hospital or contact the poison control centers:
Hospital de Niños Dr. Ricardo Gutiérrez: Ph #: (011) 4962-6666/2247
Hospital Pedro de Elizalde: Ph #: (011) 4300-2115 / 4362-6063
Hospital Dr. Juan A. Fernández: Ph #.: (011) 4808-2655
Hospital Dr A. Posadas Ph #.: (011) 4654-6648/ 4658-7777 / 0800-3330160

DOSAGE FORMS
KEMFLUD – Fulvestrant 250 mg / 5 ml – Solution for Injection.
Package containing 2 vials

STORE AT A TEMPERATURE BETWEEN 2 ° C AND 8 ° C
PROTECTED FROM LIGHT IN ITS ORIGINAL PACKAGING
KEEP OUT OF THE REACH OF CHILDREN.
Do not use after the expiry date
"This medication must be used exclusively under a medical prescription and cannot be repeated without a new prescription"

Medicinal Specialty authorized by the Ministry of Health (ANMAT).
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