250mm

For the use of a Registered Medical Practitioner or a hospital or a laboratory only.

# ℞ Fulvestrant Injection (250 mg/5 ml)

# FULVEKAST™

250 mg/Pre-filled Syringe

For Intra-muscular use only

For single use only

**COMPOSITION**

Each ml contains:

| | |
|---|---|
| Fulvestrant IP | 50 mg |
| Ethanol (96%) USP | 10 % w/v |
| Excipients | qs |

**DESCRIPTION:**

Fulvestrant is fulvestrant injection, an estrogen receptor antagonist.

**CLINICAL PHARMACOLOGY**

**A. Mechanism of action**[1,4,6]

Fulvestrant is an estrogen receptor (ER) antagonist without known estrogen agonist effect, that binds to the estrogen receptor in a competitive manner with affinity comparable to that of estradiol but greater than that of tamoxifen and down-regulates the ER protein in human breast cancer cells.

**B. Pharmacodynamics**[4]

In clinical studies in postmenopausal women with primary breast cancer treated with single doses of Fulvestrant, there are evidence of increasing down-regulation of ER with increasing dose. This was associated with a dose-related decrease in the expression of the progesterone receptor, an estrogen-regulated protein.

**C. Pharmacokinetics**[2, 3, 4,6]

- **Absorption**: The drug has poor oral bio-availability. Following intramuscular administration, it takes 7 days for peak plasma levels to be achieved, and they are maintained for at least a month. The half life is about 40 days.
- **Distribution:** The apparent volume of distribution at steady state is approximately 3 to 5 L/kg. This suggests that distribution is largely extravascular. Fulvestrant is highly (99%) bound to plasma proteins; VLDL, LDL and HDL lipoprotein fractions appear to be the major binding components.
- **Metabolism**: Cytochrome P-450 (CYP3A4) is the only P-450 isoenzyme involved in the oxidation of fulvestrant.
- **Excretion:** Fulvestrant is rapidly cleared by the hepatobiliary route with excretion primarily via the feces (approximately 90%). Renal elimination is less than 1%. After an intramuscular injection of 250 mg, the clearance (Mean ± SD) observed 690 ± 226 mL/min with an apparent half-life about 40 days.

**INDICATION**[4,6]

Fulvestrant is indicated for the treatment of hormone receptor positive Metastatic Breast Cancer in postmenopausal women with disease progression following antiestrogen therapy.

**DOSAGE AND ADMINISTRATION**[4,6]

Fulvestrant is given as intramuscular injection only.

**A. Recommended Dose:** The recommended dose is 500 mg to be administered intramuscularly into the buttocks slowly (1-2 minutes per injection) as two 5 ml injections, one in each buttock on days 1, 15, 29 and once monthly thereafter.

**B. Dose Adjustments:**

**Dosage adjustment for hepatic impairment:** A dose of 250 mg is recommended for patients with moderate hepatic impairment (Child-Pugh class B) to be administered intramuscularly on days 1, 15, 29 and once monthly thereafter. No dosage adjustment needed in patients with mild hepatic impairment. Use with caution in patients with severe hepatic impairment as no studies are available.

**Dosage adjustment for renal impairment:** No adjustments needed.

**DOSAGE FORM & STRENGTHS**

Fulvestrant an injection for intramuscular administration, is supplied as 250 mg PFS.

**CONTRAINDICATIONS**[4]

Fulvestrant is contraindicated in patients with a known hypersensitivity to the drug or to any of its components. Hypersensitivity reactions, including urticaria and angioedema, have been reported in association with Fulvestrant.

**WARNINGS AND PRECAUTIONS**[4,6]

**A. Blood disorder**: Because Fulvestrant is administered intramuscularly; it should be used with caution in patients with coagulopathy, thrombocytopenia, or anticoagulant use. Fulvestrant may cause bleeding, bruising and hematomas in these patients.

**B. Hepatic Impairment**: Fulvestrant exposure was increased in patients with moderate hepatic impairment, therefore a dose of 250 mg is recommended.

**C. The safety and efficacy:** The safety and efficacy of fulvestrant have not been established in patients with severe hepatic disease, including biliary tract disease, hyperbilirubinemia (cholestasis) or jaundice.

**D. Use in Pregnancy**: Refer from Use In Specific Populations.

**E. Use in lactation:** Refer from Use In Specific Populations.

**ADVERSE REACTIONS**[4]

| Adverse effect | >10 % | 1% to 10% |
|---|---|---|
| Gastrointestinal | Nausea, vomiting, constipation, diarrhea, abdominal pain. | - |
| Central nervous system | Headache | - |
| Endocrine | Hot flushes | - |
| Neuromuscular and Skeletal | Back pain | - |
| Respiratory | Pharyngitis | - |
| Injection site reaction | - | Mild transient pain and inflammation |
| Flu-like symptoms | - | Asthenia, myalgias, arthralgias |

<1%- Vaginal bleeding, thromboembolism, vertigo, leucopenia. Hypersensitivity reactions such as angioedema have been infrequently reported.

100mm

250mm

Post- marketing surveillance: Hyperbilirubinemia, elevated hepatic enzymes (e.g. gamma glutamyl transferase), hepatitis and hepatic failure.

**DRUG INTERACTIONS**[4]

No drug interactions have been documented with fulvestrant. Fulvestrant is partly metabolized by cytochrome P450 (CYP3A4) in-vitro. Clinical studies of potent CYP3A4 inhibitors on the pharmacokinetics of fulvestrant have not been studied. A clinical study with rifampin, an inducer of CYP3A4, showed no effect on the pharmacokinetics of fulvestrant. Omacetaxine may theoretically increase the risk of infections. No other specific major drug interaction is known to exist. Caution should be maintained if patient is taking warfarin which may increase the risk of bleeding.

**USE IN SPECIFIC POPULATIONS**[4]

**A. Pregnancy**

**Pregnancy Category D**. Fulvestrant can cause fetal harm or loss when administered to a pregnant woman. Women of childbearing potential should be advised not to become pregnant while receiving Fulvestrant. If Fulvestrant is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be informed of potential risk to the fetus.

**B. Nursing mothers**

It is not known whether Fulvestrant is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from fulvestrant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**C. Paediatric use**

The safety and efficacy of fulvestrant in paediatric patients have not been established.

**D. Geriatric use**

No differences in fulvestrant pharmacokinetics related to age have been observed in adults.

**OVERDOSAGE** [5]

Animal studies have shown no effects other than those related directly or indirectly to antiestrogen activity with intramuscular doses of fulvestrant higher than the recommended human dose. There is no clinical experience with overdosage in humans. No adverse reactions were seen in healthy male and female volunteers who received intravenous fulvestrant, which resulted in peak plasma concentrations at the end of the infusion, that were approximately 10 to 15 times those seen after intramuscular injection.

**STORAGE**

Store at temperature between 2ºC to 8ºC.

**PRESENTATION**

5 ml prefilled USP Type I glass syringe containing 250 mg of Fulvestrant packed in a mono carton along with pack insert & a needle.

**PATIENT EDUCATION**[4]

- Physician should be informed about any of underlying conditions such as bleeding problems, liver disease, low level of platelets, an unusual or allergic reaction to fulvestrant.
- Women of childbearing potential are advised not to become pregnant while receiving Fulvestrant. Fulvestrant can cause fetal harm when administered to pregnant woman [see Warnings and Precautions and Use in Specific Populations].
- Fulvestrant may interact with medicines that treat or prevent blood clots like warfarin, enoxaparin and dalteparin.
- Allergic reaction like skin rash, itching or hives, swelling of the face, lips or tongue, feeling faint or lightheaded, falls, fever or flu-like symptoms, sore throat, vaginal bleeding should be reported to doctor immediately.

**REFERENCES:**


1. Br J Cancer. 2004 March; 90(S1): S2–S6.
2. Drugs, Volume 64, March 2004 , pp. 633-648(6)
3. British Journal of Cancer (2004) 90, S7–S10.
4. Fulvestrant Monograph at MD Consultant. (www.mdconsultant.com-last accessed on-29.04.2013)
5. www.rxlist .com (Last accessed on-29.04.2013)
6. The Chemotherapy source book by Michael C. Perry, 5th edition, Page- 692



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