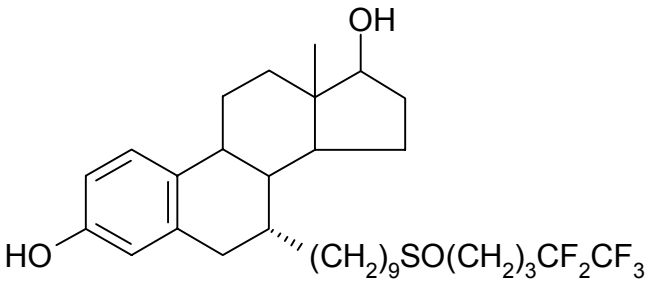
Rev 04/25/02

FASLODEX
(fulvestrant) Injection

DESCRIPTION

FASLODEX® (fulvestrant) Injection for intramuscular administration is an estrogen receptor antagonist without known agonist effects. The chemical name is 7-alpha-[9-(4,4,5,5,5-penta fluoropentylsulphinyl) nonyl]estra-1,3,5-(10)- triene-3,17-beta-diol. The molecular formula is $C_{32}H_{47}F_5O_3S$ and its structural formula is:



Fulvestrant is a white powder with a molecular weight of 606.77. The solution for injection is a clear, colorless to yellow, viscous liquid.

Each injection contains as inactive ingredients: Alcohol, USP, Benzyl Alcohol, NF, and Benzyl Benzoate, USP, as co-solvents, and Castor Oil, USP as a co-solvent and release rate modifier.

FASLODEX is supplied in sterile single patient pre-filled syringes containing 50-mg/mL fulvestrant either as a single 5 mL or two concurrent 2.5 mL injections to deliver the required monthly dose. FASLODEX is administered as an intramuscular injection of 250 mg once monthly.

CLINICAL PHARMACOLOGY

Mechanism of Action

Many breast cancers have estrogen receptors (ER), and the growth of these tumors can be stimulated by estrogen. Fulvestrant is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner with affinity comparable to that of estradiol. Fulvestrant downregulates the ER protein in human breast cancer cells.

doses of FASLODEX 15-22 days prior to surgery, there was 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. These effects on the ER pathway were also associated with a decrease in Ki67 labeling index, a marker of cell proliferation.

In vitro studies demonstrated that fulvestrant is a reversible inhibitor of the growth of tamoxifen-resistant, as well as estrogen-sensitive human breast cancer (MCF-7) cell lines. In *in vivo* tumor studies, fulvestrant delayed the establishment of tumors from xenografts of human breast cancer MCF-7 cells in nude mice. Fulvestrant inhibited the growth of established MCF-7 xenografts and of tamoxifen-resistant breast tumor xenografts. Fulvestrant resistant breast tumor xenografts may also be cross-resistant to tamoxifen.

Fulvestrant showed no agonist-type effects in *in vivo* uterotropic assays in immature or ovariectomized mice and rats. In *in vivo* studies in immature rats and ovariectomized monkeys, fulvestrant blocked the uterotrophic action of estradiol. In postmenopausal women, the absence of changes in plasma concentrations of FSH and LH in response to fulvestrant treatment (250 mg monthly) suggests no peripheral steroidal effects.

Pharmacokinetics

Following intravenous administration, fulvestrant is rapidly cleared at a rate approximating hepatic blood flow (about 10.5 ml plasma/min/Kg). After an intramuscular injection plasma concentrations are maximal at about 7 days and are maintained over a period of at least one month, with trough concentration about one-third of Cmax. The apparent half-life was about 40 days. After administration of 250 mg of fulvestrant intramuscularly every month, plasma levels approach steady-state after 3 to 6 doses, with an average 2.5 fold increase in plasma AUC compared to single dose AUC and trough levels about equal to the single dose Cmax (see **Table 1**).

Table 1: Summary of fulvestrant pharmacokinetic parameters in postmenopausal advanced breast cancer patients after intramuscular administration of a 250 mg dose (Mean ± SD)

	C_{max} ng/ml	C_{min} ng/ml	AUC ng.d/ml	t½ days	CL ml/min
Single dose	8.5 ± 5.4	2.6 ± 1.1	131± 62	40 ± 11	690 ± 226
Multiple dose steady state	15.8 ± 2.4	7.4 ± 1.7	328 ± 48		

Fulvestrant was subject to extensive and rapid distribution. The apparent volume of distribution at steady state was approximately 3 to 5 L/kg. This suggests that distribution is largely extravascular. Fulvestrant was highly (99%) bound to plasma proteins; 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.

Metabolism and Excretion:

intramuscular and intravenous administration of ^{14}C-labeled 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, 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. Identified metabolites are either less active or exhibit similar activity to fulvestrant in antiestrogen models. Studies using human liver preparations and recombinant human enzymes indicate that cytochrome P-450 3A4 (CYP 3A4) is the only P-450 isoenzyme involved in the oxidation of fulvestrant; however, the relative contribution of P-450 and non-P-450 routes *in vivo* is unknown.

Fulvestrant was rapidly cleared by the hepatobiliary route with excretion primarily via the feces (approximately 90%). Renal elimination was negligible (less than 1%).

Special Populations:

Geriatric-- In patients with breast cancer, there was no difference in fulvestrant pharmacokinetic profile related to age (range 33 to 89 years).

Gender-- Following administration of a single intravenous dose, there were no pharmacokinetic differences between men and women or between premenopausal and postmenopausal women. Similarly, there were no apparent differences between men and postmenopausal women after intramuscular administration.

Race-- In the advanced breast cancer treatment trials, the potential for pharmacokinetic differences due to race have been evaluated in 294 women including 87.4% Caucasian, 7.8% Black, and 4.4% Hispanic. No differences in fulvestrant plasma pharmacokinetics were observed among these groups. In a separate trial, pharmacokinetic data from postmenopausal ethnic Japanese women were similar to those obtained in non-Japanese patients.

Renal Impairment-- Negligible amounts of fulvestrant are eliminated in urine; therefore, a study in patients with renal impairment was not conducted. In the advanced breast cancer trials, fulvestrant concentrations in women with estimated creatinine clearance as low as 30 mL/min were similar to women with normal creatinine.

Hepatic Impairment-- Fulvestrant is metabolized primarily in the liver. In clinical trials in patients with locally advanced or metastatic breast cancer, pharmacokinetic data were obtained following administration of a 250 mg dose of FASLODEX to 261 patients classified as having normal liver function and to 24 patient with mild impairment. Mild impairment was defined as an alanine aminotransferase concentration (at any visit) greater than the upper limit of the normal (ULN) reference range, but less than 2 times the ULN; or if any 2 of the following 3 parameters were between 1- and 2-times the ULN: aspartate aminotransferase, alkaline phosphatase, or total bilirubin.

There was no clear relationship between fulvestrant clearance and hepatic impairment and the safety profile in patients with mild hepatic impairment was similar to that seen in patients with no hepatic impairment. Safety and efficacy have not been evaluated in patients with moderate to severe hepatic impairment (see **PRECAUTIONS-Hepatic Impairment** and **DOSAGE AND ADMINISTRATION-Hepatic Impairment** sections).

Pediatric--The pharmacokinetics of fulvestrant have not been evaluated in pediatric patients.

Drug-Drug Interactions

There are no known drug-drug interactions. Fulvestrant does not significantly inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2C19, 2D6, and 3A4 *in vitro*, and studies of co-administration of fulvestrant with midazolam indicate that therapeutic doses of fulvestrant have no inhibitory effects on CYP 3A4 or alter blood levels of drug metabolized by that enzyme. Also, although fulvestrant is partly metabolized by CYP 3A4, a clinical study with rifampin, an inducer of CYP 3A4, showed no effect on the pharmacokinetics of fulvestrant. Clinical studies of the effect of strong CYP 3A4 inhibitors on the pharmacokinetics of fulvestrant have not been performed.

Clinical Studies

Efficacy of FASLODEX was established by comparison to the selective aromatase inhibitor anastrozole in two randomized, controlled clinical trials (one conducted in North America, the other in Europe) in postmenopausal women with locally advanced or metastatic breast cancer. All patients had progressed after previous therapy with an antiestrogen or progestin for breast cancer in the adjuvant or advanced disease setting. The majority of patients in these trials had ER+ and/or PgR+ tumors. Patients who had ER-/PgR- or unknown disease must have shown prior response to endocrine therapy.

In both trials, eligible patients with measurable and/or evaluable disease were randomized to receive either FASLODEX 250 mg intramuscularly once a month (28 days $\pm$ 3 days) or anastrozole 1 mg orally once a day. All patients were assessed monthly for the first three months and every three months thereafter. The North American trial was a double-blind, randomized trial in 400 postmenopausal women. The European trial was an open, randomized trial conducted in 451 patients. Patients on the FASLODEX arm of the North American trial received two separate injections (2 X 2.5 ml), whereas FASLODEX patients received a single injection (1 X 5 ml) in the European trial. In both trials, patients were initially randomized to a 125 mg per month dose as well, but interim analysis showed a very low response rate and low dose groups were dropped.

The effectiveness endpoints were response rates (RR), based on the Union Internationale Contre le Cancer (UICC) criteria, and time to progression (TTP). Survival time was also determined. Confidence intervals (95.4%) were calculated for the difference in RR between the FASLODEX and anastrozole groups. The hazard ratio for an unfavorable event, (such as disease progression or death) between FASLODEX and anastrozole groups was also determined.

women randomized to FASLODEX 250 mg or anastrozole 1 mg.

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