

LETROZOL SERVYCAL

LETROZOLE 2.5 mg

Coated Tablets

Sale under filed prescription

Made in Argentina

QUALI-QUANTITATIVE COMPOSITION:

Each coated tablet contains:

Letrozole.....	2.50 mg
Lactose monohydrate	60.00 mg
Sodium starch glycollate.....	3.00 mg
PVP K-30	4.00 mg
Microcrystalline cellulose	23.00 mg
Magnesium stearate	1.00 mg
Pregelatinized starch	10.00 mg
Hydroxypropyl methylcellulose	3.25 mg
Polyethylene glycol 6000	2.00 mg
Titanium dioxide.....	0.75 mg

DRUG CATEGORY:

Antiestrogenic.

L02B G04

PHARMACOLOGY

• PHARMACODYNAMICS:

Letrozole is an antineoplastic; is non-steroidal aromatase inhibitor (inhibitor of estrogen biosynthesis). It inhibits the aromatase enzyme by competitively binding to the heme of the cytochrome P450 subunit of the enzyme, resulting in a reduction of estrogen biosynthesis in all tissues.

Studies with Letrozole in healthy post-menopausal women have shown that single doses of 0.1, 0.5 and 2.5 mg suppress estrone from 75% to 78% and serum estradiol by 78% from baseline. Maximum suppression was achieved in 48 to 78 hours.

In post-menopausal women with advanced breast cancer, daily doses of 0.1 to 5 mg suppress estradiol, estrone and estrone sulphate plasma levels by 75% to 95% from baseline in all treated women. With doses of 0.5 mg or more, many levels of estrone were below the limit of detection of the assays. Thus, higher estrogen suppression is achieved throughout treatment with these doses.

Letrozole is highly specific in the inhibition of aromatase activity. Impairment of adrenal steroidogenesis has not been observed. No clinically significant changes were found in plasma levels of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxy-progesterone and ACTH, or in plasma renin activity in post-menopausal women treated with 0.1 to 5 mg of Letrozole. The stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0.1, 0.25, 1, 2.5, and 5 mg did not indicate any reduction of aldosterone or cortisol activity. Therefore, glucocorticoid or mineralocorticoid supplementation is not required.

In healthy post-menopausal women, no changes were observed in plasma androgen concentrations (androstenedione and testosterone) after single letrozole doses of 0.1, 0.5 and 2.5 mg. No changes were observed either in post-menopausal women treated with daily doses of 0.1 to 5 mg. This indicates that the inhibition of estrogen biosynthesis do not lead to the accumulation of androgenic precursors.

- **PHARMACOKINETICS:**

Absorption: letrozole is rapidly and completely absorbed from the gastrointestinal tract. The mean absolute bioavailability is about 99.9%. Food slightly decreases the rate of absorption, but the extent of absorption (AUC) does not change. This minor effect is not clinically relevant, thus letrozole may be taken with or without food.

Distribution: plasma protein binding is approximately 60%, mainly to albumin (55%). The concentration of letrozole in erythrocytes is 80% of that in plasma. Systemic exposure to metabolites is low. It is rapidly distributed into tissues and its volume of apparent distribution at steady state is 1.87 ± 0.47 L/kg.

Metabolism and elimination: metabolism to a pharmacologically-inactive carbinol metabolite is the main elimination pathway of letrozole (Cl_m = 2.1 L/h), but it is relatively slow if compared to the hepatic blood flow (90 L/h). The cytochrome P450 isoenzymes 3A4 and 2A6 can convert letrozole to this metabolite. The formation of minor unidentified metabolites and direct renal and fecal excretion play a minor role in the overall elimination of letrozole. About 75% of the radioactivity recovered in urine up to 216 hours (84.7 ± 7.8 % of dose) was in the form of glucuronide of the carbinol metabolite, 9% of 2 unidentified metabolites, and 6% of unchanged letrozole. The apparent terminal elimination half-life in plasma is about 2 days. After daily doses of 2.5 mg steady-state levels are achieved between the 2nd and 6th week.

Plasma concentrations at steady state are 7 times higher than concentrations measured after the administration of a single dose of 2.5 mg, and are between 1.5 and 2 times higher than said steady-state values from the concentrations measured after a single dose. No continuous accumulation of letrozole occurs because steady-state levels are maintained on the long term.

Patients with hepatic and/or renal impairment: in studies in women with varying degrees of hepatic impairment, mean AUC values of patients with moderate impairment were 37% higher than in normal individuals. In studies in women with 24-hour creatinine clearance, between 9 to 116 mL/min, after a single dose of 2.5 mg, no effect was observed on letrozole pharmacokinetics.

In a study conducted in women with advanced breast cancer, renal or hepatic impairment had no effect on letrozole concentration.

INDICATIONS

Letrozole is indicated for the treatment of advanced breast cancer in women with natural or artificially induced post-menopausal status, who had disease progression or recurrence following antiestrogen therapy.

DOSAGE

Post-menopausal and elderly patients: The recommended dose is 2.5 mg once daily. Treatment should continue, at physician's discretion, until tumor progression is evident. No dose adjustments are required for elderly patients.

Patients with hepatic and/or renal impairment: No dose adjustments are required for patients with hepatic or renal impairment (creatinine clearance = 10 mL/min or higher).

If you missed a dose and you are not close to the time of your next dose, you can take the as soon as you remember. Otherwise, skip the missed dose without worrying. Never double dose.

ADVERSE REACTIONS

In general, reported adverse reactions were mild to moderate and rarely severe enough to interrupt treatment. Most of them may be due to pharmacological consequences of estrogen deprivation or to underlying diseases.

The following were the more frequent adverse reactions, with an incidence of up to 2.5%: headache, nausea, vomiting, dizziness, peripheral edema, fatigue, hot flashes, hair thinning, erythematous rash, maculopapular rash, weight gain, hyperphagia, pain in arms and legs, skeletal pain, lumbar back pain, anorexia, vaginal hemorrhage, leucorrhea, constipation, increased sweating, dyspnea, thrombophlebitis, hypertension, pruritus.

The following adverse reactions were reported with an incidence lower than 2.5%: weight loss, generalized edema.

PRECAUTIONS AND WARNINGS

Pregnancy and breastfeeding: There are not enough studies to establish the safety of letrozole in pregnant and breastfeeding women. Animal reproduction studies have not been completed. Thus, this medicine is contraindicated during these periods.

Pediatric use: this medicine should not be used in girls.

Effects on the ability to drive and operate machinery: fatigue and dizziness have been observed with use in some patients. Patients should be advised that physical and mental abilities may be impaired; therefore it is recommended to avoid tasks requiring full alertness.

Elderly patients: no dose adjustments are required for elderly patients.

Important: letrozole should not be used in women who have menstruations. If women have severe renal impairment, they should consult their physician to determine treatment conditions. Before initiating letrozole treatment, the physician should become aware of patient's history, including past or existing medical problems, and also whether the patient is taking other medicines.

DRUG-DRUG INTERACTIONS

There is no evidence to date on the unwanted effects of letrozole whenever it is administered in combination with other medicines.

The coadministration of letrozole with cimetidine and warfarin did not result in clinically significant effects.

Moreover, there were no relevant interactions when letrozole was given concomitantly with: omeprazole, paracetamol, ibuprofen, furosemide, diclofenac sodium, barbiturates, and benzodiazepines.

There is no evidence to date on the use of letrozole in combination with other antineoplastic agents.

CONTRAINDICATIONS

Hypersensitivity to active ingredient or to any excipient of the composition. Pre-menopausal endocrine status, pregnancy, breastfeeding.

OVERDOSAGE

There is no medicine to date with letrozole overdose. Treatment should be symptomatic and supportive. There is no specific treatment.

If an overdose occurs, go to the nearest Hospital or contact Toxicology Centers:

Hospital de Niños Dr. Ricardo Gutiérrez: Ph: + 54 (11) 4962-6666 / 2247

Hospital Dr. Juan P. Garrahan: Ph: + 54 (11) 4941-6191 / 6012

Hospital Dr. Juan A. Fernández: Ph: + 54 (11) 4801-5555

Hospital A. Posadas: Ph: + 54 (11) 4654-6648 / 4658-7777

Presentation: carton containing 30 tablets.

KEEP AT ROOM TEMPERATURE UP TO 30° C, PROTECTED FROM LIGHT.

KEEP OUT OF REACH OF CHILDREN

“THIS MEDICINE SHALL BE USED UNDER MEDICAL PRESCRIPTION AND IT SHALL NOT BE REPEATED WITHOUT A NEW PRESCRIPTION”

Medicinal Specialty authorized by the Argentine Ministry of Health (A.N.M.A.T.).
Certificate No. 52744

Technical Director: Pamela Carla Marcuzzi – Pharmacist- Biochemist

SERVYCAL S.A.

José Ingenieros 2489 – (B1636EPS) – Olivos

Buenos Aires – Argentina

Ph/Fax: + 54 (11) 4794-9382

www.servycal.com

Manufactured at:

Arengreen 830 – (C1405CYH) - C.A.B.A. - Argentina

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