GCTROL

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COMPOSITION

Each film-coated contains

Letrozole USP	2.5 mg
Excipients	Q.S.

Colours: Yellow Oxide of Iron & Titanium Dioxide

DOSAGE FORM

Tablets for oral use.

PHARMACOLOGY

Pharmacodynamics

Letrozole is a specific nonsteroidal aromatase inhibitor. It inhibits the aromatase enzyme by competitively binding to the haem of the cytochrome P450 subunit of the enzyme, resulting in a reduction of estrogen biosynthesis in all tissues.

Induction of ovulation in Infertility

Estrogen exerts a negative feedback on the hypothalamic-pituitary axis and decreases the release of FSH from the pituitary gland. Letrozole acts by blocking the synthesis of estrogen. Administration of letrozole in the early part of the menstrual cycle results in release of FSH from the pituitary gland. Letrozole acts by blocking the feedback, thereby increasing gonadotropin secretion and resulting in stimulation of ovarian follicle. Letrozole leads to induction of ovulation in women with anovoluatory infertility. Letrozole does not deplete estrogen receptor or produce a negative effect on the endometrium. Addition of letrozole to gonadotropins decreases gonadotropin requirements, increases the number of preovulatory follicles, and decreases endometrial thickness without a negative effect on pregnancy rates.

Breast cancer

Letrozole exerts its antitumour effect by depriving estrogen dependent breast cancer cells of their growth stimulus. In postmenopausal women, estrogens are derived mainly from the action of the aromatase enzyme, which converts adrenal androgens-primarily androstenedione and testosterone-to-estrone (E). The suppression of estrogen biosynthesis in the peripheral tissues and the malignant tissues can be achieved by specifically inhibiting the aromatase enzyme. Impairment of adrenal steroidogenesis has not been observed.

Pharmacokinetics

Letrozole is rapidly and completely absorbed from the gastrointestinal tract and absorption is not affected by food. It is metabolized slowly to an inactive metabolite whose glucuronide conjugate is excreted renally, representing the major clearance pathway. About 90% of radiolabeled letrozole is recovered in urine. Letrozole's terminal elimination half-life is about 2 days and steady-state plasma concentration after daily 2.5 mg dosing is reached in 2-6 weeks. Plasma concentrations at steady state are 1.5 to 2 times higher than predicted from the concentrations measured after a single dose, indicating a slight non-linearity in the pharmacokinetics of letrozole upon daily administration of 2.5 mg. These steady-state levels are maintained over extended periods, however, and continuous accumulation of letrozole does not occur. Letrozole is weakly protein bound and has a large volume of distribution (approximately 1.9 L/kg).

Metabolism and Excretion

Metabolism to a pharmacologically-inactive carbinol metabolite (4,4′ -methanolbisbenzonitrile) and renal excretion of the glucuronide conjugate of this metabolite is the major pathway of letrozole clearance. Of the radiolabel recovered in urine, at least 75% was the glucuronide of the carbinol metabolite, about 9% was two unidentified metabolites, and 6% was unchanged letrozole.
In human microsomes with specific CYP isozyme activity, CYP3A4 metabolized letrozole to the carbinol metabolite while CYP2A6 formed both this metabolite and its ketone analog. In human liver microsomes, letrozole strongly inhibited CYP2A6 and moderately inhibited CYP2C19.

INDICATIONS

GCTROL is indicated for:

Induction of ovulation - in anovulatory infertility, for the induction of ovulation in women with anovulatory infertility.

Breast cancer - for the treatment of advanced/metastatic breast cancer (hormone receptor positive or receptor status unknown) in post-menopausal women as first line treatment.

DOSAGE AND ADMINISTRATION

Induction of ovulation in anovulatory infertility

Only for women of reproductive age with anovulatory infertility, the recommended dosage of **GCTROL** is 2.5 mg once daily for 5 days (days 3 to 7 of the menstrual cycle); for 3 consecutive cycles or till occurrence of pregnancy whichever is earlier. If ovulation does not occur after 3 courses of therapy, further treatment with letrozole is not recommended and the patient should be reevaluated.

Breast cancer

The recommended dose of **GCTROL** is 2.5 mg once daily. Treatment with **GCTROL** should continue as long as tumor response is seen.

CONTRAINDICATIONS

Known or suspected hypersensitivity to letrozole, other aromatase inhibitors, or to any of their ingredients, pregnancy, lactation, severe hepatic dysfunction; in the presence of an ovarian cyst, except polycystic ovary, since further enlargement of the cyst may occur.

WARNINGS AND PRECAUTIONS

General

Since fatigue and dizziness have been observed with the use of letrozole and somnolence was uncommonly reported, caution is advised when driving or using machinery. No dose related effect of letrozole on any haematologic or clinical chemistry parameter was evident in studies. Moderate decreases in lymphocyte counts, of uncertain clinical significance, were observed in some patients receiving letrozole 2.5 mg. This depression was transient in about half of those affected. Increases
in SGOT, SGPT and gamma GT > 5 times the upper limit of normal (ULN) and of bilirubin > 1.5 times the ULN were most often associated with metastatic disease in the liver.During adjuvant treatment with Letrozole, women with osteoporosis or at risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry e.g. DEXA scanning at the commencement of treatment.

Induction of ovulation in anovulatory infertility

Patient selection for the treatment of infertility should be done with care and pelvic examination should be performed prior to letrozole administration and before each subsequent course. The patient should be instructed to inform the doctor of any abdominal or pelvic pain, weight gain or discomfort. Endometrial

biopsy should always be performed prior to letrozole therapy in this population. Caution should be exercised when using letrozole in patients with uterine fibroids
due to the potential for further enlargement of the fibroids.

Drug interactions

Clinical interaction studies with cimetidine and warfarin indicated that the coadministration of letrozole with these drugs does not result in clinically significant drug reactions, even though cimetidine is a known inhibitor of one of the cytochrome P450 isoenzymes capable of metabolising letrozole in vitro. Letrozole inhibits in vitro the cytochrome P450-isoenzymes 2A6 and moderately
2C19, however, CYP2A6 does not play a major role in drug metabolism. Coadministration of letrozole and tamoxifen 20 mg daily resulted in a reduction of letrozole plasma levels of 38% on average. In many clinical studies letrozole has been safely coadministered and/or any untoward interaction reported. There was no evidence of other clinically relevant interaction in patients receiving other commonly prescribed drugs (e.g. benzodiazepines; barbiturates; NSAIDs such
as diclofenac sodium, ibuprofen; paracetamol; furosemide; omeprazole).

Renal impairment

No dosage adjustment is required for patients with renal impairment if creatinine clearance is 10 ml/min.

Hepatic impairment

No dosage adjustment is recommended for patients with mild to moderate hepatic impairment, although letrozole blood concentrations were modestly increased in subjects with moderate hepatic impairment due to cirrhosis. The dose of letrozole in patients with cirrhosis and severe hepatic dysfunction should be reduced by 50%. Caution is recommended since letrozole elimination depends mainly on intrinsic metabolic clearance.

Pregnancy

Letrozole tablets may cause foetal harm when administered to pregnant women. Studies in rats or doses equal to or greater than 0.003 mg/kg (about 1/100 the daily maximum recommended human dose on a mg/m basis) administered during the period of organogenesis, have shown that letrozole is embryotoxic and foetotoxic, as indicated by intrauterine mortality, increased resorption, increased post-implantation loss, decreased numbers of live foetuses and foetal anomalies including absence and shortening of renal papilla, dilation of ureter, oedema and incomplete ossification of front skull and metatarsals. The use of letrozole is contraindicated during pregnancy. When being used in the treatment of infertility, to avoid inadvertent letrozole administration during early pregnancy, appropriatetests should be utilized during each treatment cycle.

Lactation

It is not known whether letrozole is excreted in human milk. Because manydrugs are excreted in human milk, letrozole should not be administered to a nursing woman.

Paediatric use

Safety and effectiveness has not been established.

Geriatric use

No modification of the normal adult dosage regimen is necessary.

UNDESIRABLE EFFECTS

Adverse events associated with letrozole are generally mild to moderate and rarely severe enough to require discontinuation. The most commonly reported adverse effects with letrozole include arthralgia, hot flushes, nausea, fatigue (lethargy, malaise, asthenia), headache, back pain.

OVERDOSAGE

There is no clinical evidence for a particular dose of letrozole resulting in life threatening symptoms. Isolated cases of letrozole overdose have been reported. In these instances, the highest single dose ingested was 6.2 mg or 25 tablets. While no serious adverse events were reported in these cases, because of the limited data available, no firm recommendations for treatment can be made. There is no specific antidote to letrozole. However, emesis could be induced if the patient is alert. Since letrozole is not highly protein bound, dialysis may be helpful.

STORAGE & HANDLING INSTRUCTIONS

Store in a cool, dry place.

PACKAGING INFORMATION

GCTROL is available in a blister pack of 5 tablets.


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