For the use of a Registered Medical Practitioner only

1.Generic Name & Brand Name

Letrozole Tablets I.P.

Letrolife ™

2.Qualitative and Quantitative Composition

Each film coated tablet contains:
Letrozole I.P. ……2.5 mg
Excipients ……q.s.
Colour: Tartrazine Lake & Titanium Dioxide I.P.

3.Dosage Form and Strength

Refer section 1 & 2

4.Clinical Particulars

4.1 Therapeutic Indication

- Indicated for induction of ovulation in anovulatory infertility.
- For first line therapy in post- menopausal women with Advanced Breast cancer
- Second line treatment of advanced breast cancer in women.

4.2 Posology and Method of Administration

Letrozole is given in the dose of 2.5 mg tablets from day 2 or 3 of the cycle for 5 day or as directed by the Gynecologist/ Registered medical practitioner.

Missed Dose

Take the missed dose as soon as it is remembered. Skip the missed dose if it is almost time for the next scheduled dose. Do not take extra medicine or double dose to make up for the missed dose.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Premenopausal endocrine status
- Premenopausal, pregnant or lactating women (see section 4.6).

4.4 Special Warnings and Precautions for Use

The medication is to be avoided if one is allergic to Letrozole or any of its ingredient or similar drugs. The medicine is likely to cause dizziness and hence driving is to be avoided. The medicines should not be taken with alcohol. Intake of Letrozole with tablets of Tamoxifen should be avoided because it can decrease the drug's effectiveness. Keep the drug out of the reach of children.

Renal impairment

Letrozole has not been investigated in a sufficient number of patients with a creatinine clearance lower than 10 ml/min. The potential risk/benefit to such patients should be carefully considered before administration of letrozole.

Hepatic impairment

In patients with severe hepatic impairment (Child-Pugh C), systemic exposure and terminal half-life were approximately doubled compared to healthy volunteers. Such patients should therefore be kept under close supervision.

Bone effects

Letrozole is a potent oestrogen-lowering agent. Women with a history of osteoporosis and/or fractures, or who are at increased risk of osteoporosis, should have their bone mineral density formally assessed prior to the commencement of adjuvant and extended adjuvant treatment and monitored during and following treatment with letrozole. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored. In the adjuvant setting a sequential treatment schedule (letrozole 2 years followed by tamoxifen 3 years) could also be considered depending on the patient`s safety profile.

Tendonitis and tendon rupture

Tendonitis and tendon ruptures (rare) may occur. Close monitoring of the patients and appropriate measures (e.g. immobilisation) must be initiated for the affected tendon

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine

4.5 Drug Interaction

Some drugs that may interact with this drug include estrogens (such as ethinyl estradiol, conjugated estrogens) and estrogen blockers (such as anastrozole, Tamoxifen).

4.6 Use in Special Population

Women of perimenopausal status or child-bearing potential

Letrozole should only be used in women with a clearly established postmenopausal status (see section 4.4). As there are reports of women regaining ovarian function during treatment with letrozole despite a clear postmenopausal status at start of therapy, the physician needs to discuss adequate contraception when necessary.

Pregnancy

Based on human experience in which there have been isolated cases of birth defects (labial fusion, ambiguous genitalia), letrozole may cause congenital malformations when administered during pregnancy. Studies in animals have shown reproductive toxicity. Letrozole is contraindicated during pregnancy.

Breast-feeding

It is unknown whether letrozole and its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Letrozole is contraindicated during breast-feeding.

Fertility

The pharmacological action of letrozole is to reduce oestrogen production by aromatase inhibition. In premenopausal women, the inhibition of oestrogen synthesis leads to feedback increases in gonadotropin (LH, FSH) levels. Increased FSH levels in turn stimulate follicular growth, and can induce ovulation.

Paediatric population:

The safety and effectiveness of letrozole in paediatric population has not been established and is not indicated for use in children

Geriatric population:
The safety and effectiveness of letrozole in geriatric population has not been established

4.7 Effects on Ability to Drive and Use Machines
Letrozole has minor influence on the ability to drive and use machines. Since fatigue and dizziness have been observed with the use of letrozole and somnolence has been reported uncommonly, caution is advised when driving or using machines

4.8 Undesirable Effects
Stop using the Letrozole and get emergency medical help if you have any of these signs of allergic reactions: difficulty in breathing, swelling of face, lips, tongue, or throat. Less serious side- effect may include hot flashes, warmth or redness in the face or chest, headache, muscle or joint pain, night sweats, weight gain, fatigue, weakness, nausea or swelling in hands, ankles or feet.

4.9 Overdose
There is no clinical experience of overdosage only isolated cases of overdose with letrozole have been reported. In animal studies, letrozole exhibits only a slight degree of acute toxicity. In clinical trials, the highest single and multiple doses tested in healthy volunteers was 30 mg and 5 mg, respectively, the latter also being the highest dose tested in postmenopausal breast cancer patients. Each of these doses was well tolerated. There is no clinical evidence for a particular dose of letrozole resulting in life-threatening symptoms. There is no specific antidote to letrozole. In general, supportive care, symptomatic treatment and frequent monitoring of vital signs are appropriate.

5. Pharmacological Properties
5.1 Mechanism of action
Letrozole works by inhibiting Aromatase thereby suppressing estrogen production, so the pituitary gland produces more of the hormones needed to stimulate the ovaries. These hormones, FSH (Follicle stimulating hormone) and LH (Luteinizing hormone), can cause the development of ovulation in women who are anovulatory or increase the number of eggs developing in the ovaries of women who already ovulate.
5.2 Pharmacodynamic Properties
The elimination of oestrogen-mediated growth stimulation is a prerequisite for tumour response in cases where the growth of tumour tissue depends on the presence of oestrogens and endocrine therapy is used. In postmenopausal women, oestrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens -primarily androstenedione and testosterone - to oestrone and oestradiol. The suppression of oestrogen biosynthesis in peripheral tissues and the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme. Letrozole is a non-steroidal aromatase inhibitor. It inhibits the aromatase enzyme by competitively binding to the haem of the aromatase cytochrome P450, resulting in a reduction of oestrogen biosynthesis in all tissues where present.

In healthy postmenopausal women, single doses of 0.1 mg, 0.5 mg and 2.5 mg letrozole suppress serum oestrone and oestradiol by 75%, 78% and 78% from baseline respectively. Maximum suppression is achieved in 48-78 hours.
In postmenopausal patients with advanced breast cancer, daily doses of 0.1 mg to 5 mg suppressed plasma concentration of oestradiol, oestrone, and oestrone sulphate by 75-95% from baseline in all patients treated. With doses of 0.5 mg and higher, many values of oestrone and oestrone sulphate were below the limit of detection in the assays, indicating that higher oestrogen suppression is achieved with these doses. Oestrogen suppression was maintained throughout treatment in all these patients.
Letrozole is highly specific in inhibiting aromatase activity. Impairment of adrenal steroidogenesis has not been observed. No clinically relevant changes were found in the plasma concentrations of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxyprogesterone, and ACTH or in plasma renin activity among postmenopausal patients treated with a daily dose of letrozole 0.1 to 5 mg. The ACTH stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0.1 mg,0.25 mg, 0.5 mg, 1 mg, 2.5 mg, and 5 mg did not indicate any attenuation of aldosterone or cortisol production. Thus, glucocorticoid and mineralocorticoid supplementation is not necessary.
No changes were noted in plasma concentrations of androgens (androstenedione and testosterone) among healthy postmenopausal women after 0.1 mg, 0.5 mg, and 2.5 mg single doses of letrozole or in plasma concentrations of androstenedione among postmenopausal patients treated with daily doses of 0.1 mg to 5 mg, indicating that the blockade of oestrogen biosynthesis does not lead to accumulation of androgenic precursors. Plasma levels of LH and FSH are not affected by letrozole in patients, nor is thyroid function as evaluated by TSH, T4 and T3 uptake test.

5.3 Pharmacokinetic Properties

Absorption

Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability: 99.9%). Food slightly decreases the rate of absorption (median tmax 1 hour fasted versus 2 hours fed; and mean Cmax 129 ± 20.3nmol/litre fasted versus 98.7 ± 18.6 nmol/litre fed) but the extent of absorption (AUC) is not changed. The minor effect onthe absorption rate is not considered to be of clinical relevance, and therefore letrozole may be taken without regard to mealtimes.

Distribution

Plasma protein binding of letrozole is approximately 60%, mainly to albumin (55%). The concentration of letrozole in erythrocytes is about 80% of that in plasma. After administration of 2.5 mg ^{14}C-labelled letrozole, approximately 82% of the radioactivity in plasma was unchanged compound. Systemic exposure to metabolites is therefore low. Letrozole is rapidly and extensively distributed to tissues. Its apparent volume of distribution at steady state is about 1.87 ± 0.47 L/kg.

Biotransformation

Metabolic clearance to a pharmacologically inactive carbinol metabolite is the major elimination pathway of letrozole (CL m=2.1 L/h) but is relatively slow when compared to hepatic blood flow (about 90 L/h). The cytochrome P450 isoenzymes 3A4 and 2A6 were found to be capable of converting letrozole to this metabolite in vitro, but their individual contributions to letrozole clearance in vivo have not been established. In an interaction study co-administration with cimetidine, which is known to inhibit only the 3A4 isoenzyme, did not result in a decrease in letrozole clearance suggesting that in vivo the 2A6 isoenzyme plays an important part in total clearance. In this study a slight decrease in AUC and increase in Cmax were observed.
Formation of minor unidentified metabolites and direct renal and faecal excretion play only a minor role in the overall elimination of letrozole. Within 2 weeks after administration of 2.5 mg

^{14}C-labelled letrozole to healthy postmenopausal volunteers, 88.2 ± 7.6% of the radioactivity was recovered in urine and 3.8 ± 0.9% in faeces. At least 75% of the radioactivity recovered in urine up to 216 hours (84.7 ± 7.8% of the dose) was attributed to the glucuronide of the carbinol metabolite, about 9% to two unidentified metabolites, and 6% to unchanged Letrozole.

Elimination

The apparent terminal elimination half-life in plasma is about 2 to 4 days. After daily administration of 2.5 mg steady-state levels are reached within 2 to 6 weeks. Plasma concentrations at steady state are approximately 7 times higher than concentrations measured after a single dose of 2.5 mg, while they are 1.5 to 2 times higher than the steady-state values 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. Since steady-state levels are maintained over time, it can be concluded that no continuous accumulation of letrozole occurs.

Linearity/non-linearity

The pharmacokinetics of letrozole were dose proportional after single oral doses up to 10 mg (dose range: 0.01 to 30mg) and after daily doses up to 1.0 mg (dose range: 0.1 to 5mg). After a 30 mg single oral dose there was a slightly dose over-proportional increase in AUC value. The dose over-proportionality is likely to be the result of a saturation of metabolic elimination processes. Steady levels were reached after 1 to 2 months at all dosage regimens tested (0.1-5.0mg daily).

6. Nonclinical Properties

6.1 Animal Toxicology or Pharmacology

In a variety of preclinical safety studies conducted in standard animal species, there was no evidence of systemic or target organ toxicity.

Letrozole showed a low degree of acute toxicity in rodents exposed up to 2000 mg/kg. In dogs, letrozole caused signs of moderate toxicity at 100 mg/kg.

In repeated-dose toxicity studies in rats and dogs up to 12 months, the main findings observed can be attributed to the pharmacological action of the compound. The no-adverse-effect level was 0.3 mg/kg in both species.

Oral administration of letrozole to female rats resulted in decreases in mating and pregnancy ratios and increases in pre-implantation loss

Both in vitro and in vivo investigations of letrozole's mutagenic potential revealed no indications of any genotoxicity.

In a 104-week rat carcinogenicity study, no treatment-related tumours were noted in male rats. In female rats, a reduced incidence of benign and malignant mammary tumours at all the doses of letrozole was found.

In a 104-week mouse carcinogenicity studies, no treatment-related tumours were noted in male mice. In female mice, a generally dose-related increase in the incidence of benign ovarian granulosa theca cell tumors was observed at all doses of letrozole tested. These tumors were considered to be related to the pharmacological inhibition of estrogen synthesis and may be due to increased LH resulting from the decrease in circulating estrogen.

Letrozole was embryotoxic and foetotoxic in pregnant rats and rabbits following oral administration at clinically relevant doses. In rats that had live foetuses, there was an increase in the incidence of foetal malformations including domed head and cervical/centrum vertebral fusion. An increased incidence of foetal malformations was not seen in the rabbit. It is not known whether this was an indirect consequence of the pharmacological properties (inhibition of oestrogen biosynthesis) or a direct drug effect (see sections 4.3 and 4.6).

Preclinical observations were confined to those associated with the recognised pharmacological action, which is the only safety concern for human use derived from animal studies.

7. Description
Letrolife is supplied for oral administration, as a film coated tablet of Letrozole. Each film coated tablet of Letrolife contains Letrozole 2.5 mg.

8. Pharmaceutical Properties

8.1 Incompatibilities
Not applicable

8.2 Shelf Life
Refer pack

8.3 Packaging Information
Refer pack

8.4 Storage and Handling Instructions
Refer pack

9.Patient Counseling

Patients should not take Letrolife:
- In case of premenopausal endocrine status, pregnant or lactating women
- If patient is allergic (hypersensitive) to any of the ingredients of this medicine

Patient should tell the doctor if she is taking or have recently taken any other medicines. In particular, estrogens and estrogen blockers may lower the effect of Letrolife

This medicine prescribed for a particular patient shouldn't be passed on to the others. It may harm them, even if their symptoms are the same.
Since fatigue and dizziness have been observed with the use of letrozole and somnolence has been reported uncommonly, caution is advised when driving or using machines. If any of the side effects gets serious, or if the patient notices any side effects not listed above, the doctor needs to be informed.

10. Details of Manufacturer

Refer Pack for manufacturing details.

Marketed By:
Abbott India Limited
Angel Space, Lifestyle Bldg. No. D-4,
Gala No. 7 to 10 & 17 to 20 Ground Floor,
107 to 110 & 117 to 120 First Floor,
Pimplas Village, Dist. Thane,
Bhiwandi - 421 302, India

11. Details of Permission or License Number
Refer Pack for Permission/License details

12. Date of Revision
Version: 3.0, dated 13/05/2024

For product complaints and queries please write to **webmasterindia@abbott.com**

Source:

- *Letrozole 2.5 mg film-coated tablets SmPC- Cipla EU Ltd*