nausea, dyspnoea, peripheral edema, coughing, constipation, vomiting, chest pain, viral infection, diarrhoea rash, abdominal pain, dyspepsia and anorexia, Dizziness, weight increase and pruritus are less commonly seen.

Overdosage

There is no clinical trial experience of overdosage. There is no specific antidote to letrozole.

Since letrozole is not highly protein bound, dialysis may be helpful. Emesis may be induced if the patient is alert. In general, supportive care and frequent monitoring of vital signs is appropriate.

Dosage and Administration

The recommended dose of Letrozole is 2.5 mg once daily. Treatment with Letrozole should continue as long as tumor response is seen. The drug should be discontinued if tumor stops responding as judged by tumor progression. For elderly patients, no modification of the normal adult dosage regimen is necessary.

No dosage adjustment is required for patients with mild to moderate hepatic impairment or renal impairment.

How supplied

HopeLet Tablets are available as 2.5 mg strength in strip of 10 tablets. 3 strips packed in a carton.

Storage :

Store protected from moisture,
at a temperature not exceeding 30^0.

Keep out of reach of children.

™Trademark applied for

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HOPE Lifecare
Unit No 209, Anandraj Industrial Estate 2nd Floor,
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Contact No.: 8080520460
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B-1, Wagle Industrial Estate,Thane 400 604.
Regd. Office: 79/87, D. Lad Path, Mumbai - 400 033.

D-190091

For the use of a Cancer Specialist or Institution or Hospital only

Letrozole Tablets IP 2.5mg

HopeLet होपलेट

Composition

Each film- coated tablet contains:
Letrozole IP 2.5mg

Clinical Pharamacology

Letrozole is a potent and highly specific nonsteroidal aromatase inhibitor. 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.

Letrozole exerts its antitumor 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 - oestrone (E1) and oestradiol (E2). The suppression of estrogen biosynthesis in the peripheral tissues and the malignant tissues can be achieved by specifically inhibiting the aromatase enzyme.

In healthy postmenopausal women, single doses of 0.1, 0.5 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 to 5 mg suppress plasma concentration of oestradiol, oestrone and oestrone sulphate by 78 - 95% from baseline in all patients treated.

Letrozole had no effect on plasma androgen concentrations (androstenedione and testosterone) among healthy postmenopausal women after single doses of 0.1 to 0.5 mg and 2.5 mg indicating that the blockade of estrogen biosynthesis does not lead to accumulation of androgenic precursors. Impairment of adrenal steroidogenesis has not been observed.

Pharmacokinetics
Letrozole is rapidly and completely absorbed from the gastro- intestinal tract (absolute bioavailability 99.9%). Food slightly decreases the rate of absorption, but the extent of absorption remains unchanged. The minor effect of the absorption is not considered to be of clinical relevance and therefore letrozole may be taken after, with or before food.

Plasma protein binding of letrozole is approximately 60%, mainly to albumin (55%). The concentration of letrozole in erthrocytes is about 80% of that in plasma.

Metabolic clearance to a pharmacologically inactive carbinol metabolite is the major elimination pathway of letrozole but is relatively slow when compared to hepatic blood flow. 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 metabolism in vivo have not been established. The apparent terminal elimination half- life in plasma is about 2 days. After daily administration of 2.5 mg of letrozole, steady- state levels are reached within 2 to 6 weeks.

Indications
HopeLet is indicated for the first line treatment of advanced/metastatic breast cancer (hormone receptor positive or receptor status unknown) in postmenopausal women.

Contraindications
HopeLet is contraindicated in known or suspected hypersensitivity to letrozole, other aromatase inhibitors, or to any of their ingredients. It is contraindicated during pregnancy, lactation and in premenopausal women. It is also contraindicated in severe hepatic dysfunction.

Warning and Precautions
In breast cancer patients with moderate hepatic dysfunction, no dosage adjustment is necessary, but caution is recommended since letrozole elimination depends mainly on intrinsic metabolic clearance.

Renal impairment (calculated creatinine clearance: 20 to 50 ml/min) did not affect steady state plasma letrozole concentration at a dose of 2.5 mg or 5 mg. Hence, no dose adjustment is necessary for such renal function impairment. It is anticipated that letrozole could be removed from blood by dialysis since it is weakly bound to plasma proteins. The potential risks and benefits to such patients should be considered carefully before prescribing letrozole.

In some cases, fatigue and dizziness have been observed with the use of Letrozole. Patients should therefore, be advised that their physical and/or mental abilities required for operating machinery or driving a car may be impaired.

Pregnancy and Lactation
Oral administration of letrozole in pregnant rats resulted in teratogenicity and maternal toxicity at 0.03 mg/kg. Embryotoxicity and fetotoxicity were seen at doses 0.003 mg/kg and there was an increase in the incidence of foetal malformation among the animals treated.

However, there are no adequate and well-controlled studies of letrozole in pregnant women and its use in these patients is not recommended.

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

Drug interactions
Clinical interaction studies with cimetidine and warfarin indicated that the co-administration of letrozole with these drugs does not result in clinically significant drug interactions, even though cimetidine is a known inhibitor of one of the cytochrome P450 isoenzymes capable of metabolizing letrozole in vitro.

Side effects
Adverse events associated with letrozole are generally mild to moderate and rarely severe enough to require discontinuation. Many can be attributed to either the underlying disease or the normal pharmacological open consequence of oestrogen deprivation (hot flushes, hair thinning). The most frequently reported adverse events are musculoskeletal pain, arthralgia, headache, fatigue,