Anastrol

Anastrozole 1 mg

COMPOSITION
Anastrol Tablet: Each film coated tablet contains Anastrozole USP 1 mg.

DESCRIPTION
Anastrozole is a non-steroidal aromatase inhibitor. It is an off-white powder with a molecular weight of 293.4. Anastrozole has moderate aqueous solubility (0.5 mg/mL at 25˚C); solubility is independent of pH in the physiological range. Anastrozole is freely soluble in methanol, acetone, ethanol, and tetrahydrofuran, and very soluble in acetonitrile.

CLINICAL PHARMACOLOGY
Mechanism of Action
Many breast cancers have estrogen receptors and growth of these tumors can be stimulated by estrogen. In postmenopausal women, the principal source of circulating estrogen (primarily estradiol) is conversion of adrenally-generated androstenedione to estrone by aromatase in peripheral tissues, such as adipose tissue, with further conversion of estrone to estradiol. Many breast cancers also contain aromatase; the importance of tumor-generated estrogens is uncertain.

Treatment of breast cancer has included efforts to decrease estrogen levels, by ovariectomy premenopausally and by use of anti-estrogens and progestational agents both pre- and post-menopausally; and these interventions lead to decreased tumor mass or delayed progression of tumor growth in some women.

Anastrol is a potent and selective non-steroidal aromatase inhibitor. It significantly lowers serum estradiol concentrations and has no detectable effect on formation of adrenal corticosteroids or aldosterone.

INDICATIONS AND USAGE
Anastrol is indicated for adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer. The effectiveness of Anastrol in early breast cancer is based on an analysis of recurrence-free survival in patients treated for a median of 31 months. Further follow-up of study patients will be required to determine long-term outcomes.
Anastrol is indicated for the first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer. Anastrol is indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following Tamoxifen therapy. Patients with ER-negative disease and patients who did not respond to previous Tamoxifen therapy rarely responded to Anastrol.

DOSAGE AND ADMINISTRATION
The dose of Anastrol is one 1 mg tablet taken once a day. For patients with advanced breast cancer, Anastrol should be continued until tumor progression.
For adjuvant treatment of early breast cancer in postmenopausal women, the optimal duration of therapy is unknown. The median duration of therapy at the time of data analysis was 31 months; the ongoing ATAC trial is planned for five years of treatment.

Patients with Hepatic Impairment: Hepatic metabolism accounts for approximately 85% of anastrozole elimination. Although clearance of Anastrol was decreased in patients with cirrhosis due to alcohol abuse, plasma Anastrol concentrations stayed in the usual range seen in patients without liver disease. Therefore, no changes in dose are recommended for patients with mild-to-moderate hepatic impairment, although patients should be monitored for side effects. Anastrol has not been studied in patients with severe hepatic impairment.

Patients with Renal Impairment: No changes in dose are necessary for patients with renal impairment.

Use in the Elderly: No dosage adjustment is necessary.

CONTRAINDICATIONS
Anastrol is contraindicated in any patient who has shown a hypersensitivity reaction to the drug or to any of the excipients.

WARNINGS
Anastrozole can cause fetal harm when administered to a pregnant woman. Anastrozole has been found to cross the placenta following oral administration of 0.1 mg/kg in rats and rabbits (about 1 and 1.9 times the recommended human dose, respectively, on a mg/m^2 basis).Studies in both rats and rabbits at doses equal to or greater than 0.1 and 0.02 mg/kg/day, respectively (about 1 and 1/3, respectively, the recommended human dose on a mg/m^2 basis), administered during the period of organogenesis showed that anastrozole increased pregnancy loss (increased pre- and/or post-implantation loss, increased resorption, and decreased numbers of live fetuses); effects were dose related in rats. Placental weights were significantly increased in rats at doses of 0.1 mg/kg/day or more.Evidence of fetotoxicity, including delayed fetal development (i.e., incomplete ossification and depressed fetal body weights), was observed in rats administered doses of 1 mg/kg/day (which produced plasma anastrozole Cssmax and AUC0-24 hr that were 19 times and 9 times higher than the respective values found in postmenopausal volunteers at the recommended dose). There was no evidence of teratogenicity in rats administered doses up to 1.0 mg/kg/day. In rabbits, anastrozole caused pregnancy failure at doses equal to or greater than 1.0 mg/kg/day (about 16 times the recommended human dose on a mg/m2 basis); there was no evidence of teratogenicity in rabbits administered 0.2 mg/kg/day (about 3 times the recommended human dose on a mg/m^2 basis).There are no adequate and well-controlled studies in pregnant women using Anastrol. If Anastrol is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

PRECAUTIONS
General: Before starting treatment with Anastrol, pregnancy must be excluded. Anastrol should be administered under the supervision of a qualified physician experienced in the use of anticancer agents.

Laboratory Tests: Patients receiving Anastrol were reported to have an elevated serum cholesterol compared to patients receiving tamoxifen (7% versus 3%, respectively).

Drug Interactions: Anastrozole inhibited in vitro metabolic reactions catalyzed by cytochromes P450 1A2, 2C8/9, and 3A4 but only at relatively high concentrations. Anastrozole did not inhibit P450 2A6 or the polymorphic P450 2D6 in human liver microsomes. Anastrozole did not alter the pharmacokinetics of antipyrine. Although there have been no formal interaction studies other than with antipyrine, based on these in vivo and in vitro studies, it is unlikely that co-administration of a 1 mg dose of Anastrozole with other drugs will result in clinically significant drug inhibition of cytochrome P450-mediated metabolism of the other drugs. An interaction study with Warfarin showed no clinically significant effect of Anastrozole on Warfarin pharmacokinetics or anticoagulant activity.
Clinical and pharmacokinetic results from the ATAC trial suggest that Tamoxifen should not be administered with Anastrozole. Co-administration of Anastrozole and Tamoxifen resulted in a reduction of Anastrozole plasma levels by 27% compared with those achieved with Anastrozole alone. Estrogen-containing therapies should not be used with Anastrol as they may diminish its pharmacologic action.

Drug/Laboratory Test Interactions: No clinically significant changes in the results of clinical laboratory tests have been observed.

Carcinogenesis: A conventional carcinogenesis study in rats at doses of 1.0 to 25 mg/kg/day (about 10 to 243 times the daily maximum recommended human dose on a mg/m^2 basis) administered by oral gavage for up to 2 years revealed an increase in the incidence of hepatocellular adenoma and carcinoma and uterine stromal polyps in females and thyroid adenoma in males at the high dose. A dose related increase was observed in the incidence of ovarian and uterine hyperplasia in females. At 25 mg/kg/day, plasma AUC $_{0\text{-}24}$hr levels in rats were 110 to 125 times higher than the level exhibited in postmenopausal volunteers at the recommended dose. A separate carcinogenicity study in mice at oral doses of 5 to 50 mg/kg/day (about 24 to 243 times the daily maximum recommended human dose on a mg/m^2 basis) for up to 2 years produced an increase in the incidence of benign ovarian stromal, epithelial and granulosa cell tumors at all dose levels. A dose related increase in the incidence of ovarian hyperplasia was also observed in female mice. These ovarian changes are considered to be rodent-specific effects of aromatase inhibition and are of questionable significance to humans. The incidence of lymphosarcoma was increased in males and females at the high dose. At 50 mg/kg/day, plasma AUC levels in mice were 35 to 40 times higher than the level exhibited in postmenopausal volunteers at the recommended dose.

Mutagenesis: Anastrol has not been shown to be mutagenic in in vitro tests (Ames and *E. coli* bacterial tests, CHO-K1 gene mutation assay) or clastogenic either in vitro (chromosome aberrations in human lymphocytes) or in vivo (micronucleus test in rats).

Impairment of Fertility: Oral administration of Anastrozole to female rats (from 2 weeks before mating to pregnancy day 7) produced significant incidence of infertility and reduced numbers of viable pregnancies at 1 mg/kg/day (about 10 times the recommended human dose on a mg/m^2 basis and 9 times higher than the AUC $_{0\text{-}24}$hr found in postmenopausal volunteers at the recommended dose).

Pregnancy
Pregnancy Category D
Nursing Mothers: It is not known if Anastrozole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Anastrol is administered to a nursing woman.

Pediatric Use: The safety and efficacy of Anastrol in pediatric patients have not been established.

Geriatric Use: In studies 0030 and 0027 about 50% of patients were 65 or older. Patients > 65 years of age had moderately better tumor response and time to tumor progression than patients < 65 years of age regardless of randomized treatment. In studies 0004 and 0005 50% of patients were 65 or older. Response rates and time to progression were similar for the over 65 and younger patients. In the ATAC adjuvant study, 35% of patients were <60 years of age; 38% were ≥60 to ≤70 years of age; and 27% were >70 years of age. The number of events by age group were insufficient to perform a subset efficacy analysis.

OVERDOSAGE
Clinical trials have been conducted with Anastrol, up to 60 mg in a single dose given to healthy male volunteers and up to 10 mg daily given to postmenopausal women with advanced breast cancer; these dosages were well tolerated. A single dose of Anastrol that results in life-threatening symptoms has not been established. In rats, lethality was observed after single oral doses that were greater than 100 mg/kg (about 800 times the recommended human dose on a mg/m2 basis) and was associated with severe irritation to the stomach (necrosis, gastritis, ulceration, and hemorrhage). In an oral acute toxicity study in the dog the median lethal dose was greater than 45 mg/kg/day. There is no specific antidote to overdosage and treatment must be symptomatic. In the management of an overdose, consider that multiple agents may have been taken. Vomiting may be induced if the patient is alert. Dialysis may be helpful because Anastrol is not highly protein bound. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

ADVERSE REACTIONS
Adjuvant Therapy: The median duration of adjuvant treatment for safety evaluation was 37.3 months, 36.9 months, and 36.5 months for patients receiving Anastrol 1 mg, Tamoxifen 20 mg, and the combination of Anastrol 1 mg plus Tamoxifen 20 mg, respectively. Adverse events occurring with an incidence of at least 5% in any treatment group during treatment or within 14 days of the end of treatment

PHARMACEUTICAL INFORMATION
Storage condition
Store in a cool and dry place, away from light. Keep out of the reach of children.

Packaging
Anastrol Tablet : Each commercial box contains 30 tablets in Alu-Alu blister pack.

Manufactured By
BEACON
Pharmaceuticals Limited
Mymensingh, Bangladesh

LF10001