For the use of a Registered Medical Practitioner or a Hospital or a Laboratory Only.

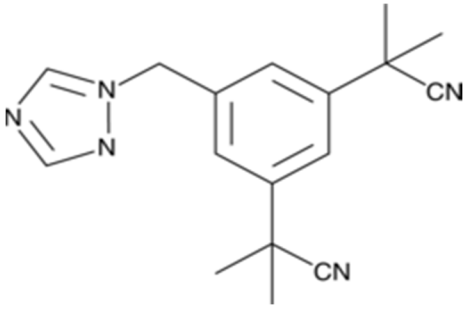
Anastrozole Tablet IP

ANASTROZ

COMPOSITION : Each film coated tablet contains Anastrozole 1mg IP.

DESCRIPTION :

Anastroz tablets for oral administration contain 1 mg of Anastrozole, a non – steroidal aromatase inhibitor. It is chemically described as 1. 3 – Benzenediacetonitrile, a, a, a'. a' –tetramethyl-5- (1H- 1 ,2,4 –triazol – I –yImethyl). Its molecular formula is C I 7 H I 9 N 5 and its structural formula is:



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 sources 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.

Anastrozole 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.

PHARMACOKINETCICS :

The orally administered Anastrozole is well absorbed into the systemic circulation with 83% to 85% of the radiolabel recovered in urine and feces. Food does not affect the extent of absorption.

Elimination of Anastrozole is primarily via hepatic metabolism (approximately 85%) and to a lesser extent, renal excretion (approximately 11%), Anastrozole has a mean terminal elimination half –life of approximately 50 hours in postmenopausal women. The major circulating metabolite of Anastrozole is triazole, lacks pharmacologic activity. The pharmacokinetic parameters are similar in patients and in

healthy postmenopausal volunteers. The pharmacokinetis of Anastrozole are linear over the dose range of 1 to 20 mg and do not change with repeated dosing. Consistent with the approximately 2 –day terminal elimination half –life, plasma concentrations approach steady – state levels at about 7 days of once daily dosing and steady- state levels are approximately three- to four- fold higher than levels observed after a single dose of Anastrozole is 40% bound to plasma proteins in the therapeutic range.

METABOLISM AND EXCRETION

Anastrozole is extensively metabolized with about 10% of the dose excreted in the urine as unchanged drug within 72 hours of dosing, and the remainder (about 60% of the dose) is excreted in urine as metabolites . Metabolism of Anastrozole occurs by N –dealkylation, hydroxylation and glucuronidation. Three metabolites of Anastrozole have been identified in human plasma and urine. The known metabolites are triazole, a glucuronide conjugate of hydroxy – Anastrozole, and a glucuronide of Anastrozole itself. Sereval minor (less than 5% of the radioactive dose) metabolites have not been identified.

Because renal elimination is not a significant pathway of elimination, total body clearance of Anastrozole is unchanged even in severe (creatinine clearance less than 30ml/min/1.73m2) renal impairment, dosing adjustment in patients with renal dysfunction is not necessary. Dosage adjustment is also unnecessary in patients with stable hepatic cirrhosis.

SPECIAL POPULATIONS GERIATRIC

Anastrozole pharmacokinetics have been investigated in postmenopausal female volunteers and patients with breast cancer. No age related effects were seen over the range < 50 to > 80 years.

RACE

Estradiol and estrone sulfate levels were similar between Japanese and Caucasian postmenopausal women who received 1 mg of Anastrozole daily for 16 days. Anastrozole mean steady- state minimum plasma concentrations in Caucasian and Japanese postmenopausal women were 25.7 and 30.4ng/ml, respectively.

RENAL INSUFFICIENCY

Anastrozole pharmacokinetics have been investigated in subjects with renal insufficiency. Anastrozole renal clearance decreased proportionally with creatinine clearance and was approximately 50% lower in volunteers with severe renal impairment (creatinine clearance < 30 ml/min/1.73m2) compared to controls. Since only about 10% of Anastrozole is excreted uncharged in the urine, the reduction in renal clearance did not influence the total body clearance.

HEPATIC INSUFFICIENCY

Hepatic metabolism accounts for approximately 85% of Anastrozole elimination. Anastrozole pharmacokinetics have been investigated in subjects with hepatic cirrhosis related to alcohol abuse. The apparent oral clearance (CL/F) of Anastrozole was approximately 30% lower in subjects with stable hepatic cirrhosis than in control subjects with normal liver function. However, plasma Anastrozole concentrations in the subjects with hepatic cirrhosis were within the range of concentrations seen in normal subjects across all clinical trials, so that no “dosage” adjustment is needed.

PHARMACODYNAMICS

EFFECT ON ESTRADIOL

Mean serum concentrations of estradiol was evaluated in multiple daily dosing trials with 0.5, 1, 3, 5, and 10mg of Anastrozole in postmenopausal women with advanced breast cancer. Clinically significant suppression of serum estradiol was seen with all doses. Doses of 1 mg and higher resulted in suppression of mean serum concentrations of estradiol to the lower limit of detection (3.7pmol/L). The recommended daily dose, Anastrozole 1 mg, reduced estradiol by approximately70% within 24 hours by approximately 80% after 14 days of daily dosing. Suppression of serum estradiol was maintained for up to 6 days after cessation of daily dosing Anastrozole 1 mg.

The effect of Anastrozole on estradiol levels in premenopausal women has not been studied. Because aromatization of adrenal androgens is not a significant sources of estradiol in premenopausal women (women with functioning ovaries as evidenced by menstruation and/ or premenopausal LH, FSH and estradiol levels), Anastrozole would not be expected to lower estradiol levels in premenopausal women.

EFFECTS ON CORTICOSTEROIDS

In multiple daily dosing trials with 3, 5 and 10 mg, the selectivity of Anastrozole was assessed by examining effects on corticosteroid synthesis. For all doses, Anastrozole did not affect cortisol or aldosterone secretion at baseline or in response to ACTH. No glucocorticoid or mineral ocorticoid replacement therapy is necessary with Anastrozole.

OTHER ENDOCRINE EFFECTS

In multiple daily dosing trials with 5 and 10 mg, thyroid-stimulating hormone (TSH) is measured; there was no increase in TSH during the administration of Anastrozole. Anastrozole does not possess direct progestogenic, androgenic, or estrogenic activity in animals, but does perturb the circulating levels of progesterone, androgens, and estrogens.

INDICATIONS

Anastrozole is indicated for adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.

Anastrozole is indicated for the first - line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer.

Anastrozole is indicated for the treatment of advanced breast cancer in postmenopausal women with dieases progression following tamoxifen therapy. Patients with ER-negative disease and paitents who did not respond to previous tamoxifen therapy rarely responded to Anastrozole.

DOSAGE AND ADMINISTRATION

The dose of Anastrozole is one 1 mg tablet taken once a day. For patients with advanced breast cancer. Anastrozole should be continued until tumor progression.

For adjuvant treatment of early breast cancer in postmenopausal women, the optimal duration of therapy is unknown. In the ATAC trial Anastrozole was administered for five years.

PATIENTS WITH HEPATIC IMPAIRMENT

Hepatic metabolism accounts for approximately 85% of Anastrozole elimination. Although clearance of Anastrozole was decreased in patient with cirrhosis due to alcohol abuse, plasma Anastrozole concentrations stayed in the usual range seen in patients without liver disease. Therefore, no changes in dose are recommrnded for patients with mild - to - moderate hepatic impairment, although patients should be monitored for side effects. Anastrozole 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.

WARNINGS

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 AUCO- 24 hr that were 19 times and 9 times higher than the respective values found in the postmenopausal volunteers at recommended dose). There was no evidence of teratogenicity in rats administered dose up to 1.0 mg/kg/day. In rabbits, Anastrozole caused pregnancy failure at dose equal to or greater than 1.0 mg/kg/day (about 16 times the recommended human dose on a mg/m 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/m2 basis).

There are no adequate and well –controlled studies in pregnant women using Anastrozole.If Anastrozole is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be appraised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

PRECAUATIONS

General

Anastrozole is not recommended for use in premenopausal women as safety and efficacy has not been established Before starting treatment with Anastrozole, pregnancy must be excluded. Anastrozole should be administered under the supervision of a qualified physician experienced in the use of anticancer agents.

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 Anastrozole is administered to a nursing woman.

PEDIATRIC USE

The safety and efficacy of Anastrozole in pediatric patients have not been established.

SIDE EFFECTS

The most commonly reported events with Anastrozole are Hot flushes, Asthenia, Pain, Back pain, headache, Abdominal pain, Infection, accidental injury, Flu syndrome, Chest pain, Vasodilation, Hypertension, Nausea, Constipation, Diarrhea, Dyspepsia, Gastrointestinal disorder, Lymphoedma, Peripheral edema, Weight gain, Hypercholesteremia, Arthritis, Arthalgia, Osteoporosis, Fracture, Bone pain, Arthrosis, Depression, Insomnia, dizziness, Anxiety, Paraesthesia. Pharyngitis, increased Cough, Dyspnea, Rash , Sweating, Leukorrhea, Urinary Tract Injection, Breast pain, Vulvovaginitis, Vaginal Discharge, Hair Thinning, Vaginal bleeding, Anorexia, Vomiting, Somnolence, Erythema Multiforme, Steven Johnson syndrome, Angioedema, Utricaria, Anaphylaxis, Mood disturbances, Cataracts, Venous thromboembolic events, Ischemic cerebrovascular events, and Endometrial cancer.

DRUG INTERACTIONS

Anastrozole inhibitied 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 – medicated metabolism of the other drugs. An interaction study with warfarin showed no clinically significant effect of Anastrozole on warfarin pharmacokinetics or anticoagulant activity. At a median follow-up of 33 months, the combination of Anastrozole and tamoxifen did not demonstrate any efficacy benefit when compared with tamoxifen in all patients as well as in the hormone receptor-positive subpopulation. This treatment arm was discontinued from the trial. Based on clinical and pharmacokinetic results from the ATAC trail, tamoxifen should not be administered with Anastrozole. Co-adminintration of Anastrozole and tamoxifen resulted in reduction of Anastrozole plasma levels by 27% compared with those achieved with Anastrozole alone.

Estrogen-containing therapies should not be used with Anastrozole as they may diminish its pharmacologic action.

OVERDOSE

Clinical trials been conducted with Anastrozole 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 Anastrozole that result 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 over dosage 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 Anastrozole is not highly protein bound. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

CONTRAINDICATIONS

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

STORAGE

Store at controlled room temperature, 20-250 C (68-770 F) [see IP]

PRESENTATION

Blister of 10 Tablets

Manufactured in India by:

ZUVIUS LIFESCIENCES PVT. LTD.
A WHO-GMP CERTIFIED COMPANY
B/111, 112, 113, Kanara Business Centre,
Link Road, Ghatkopar (East), Mumbai 400075.
www.zuviuslifesciences.in