Anacare
Tablet

COMPOSITION

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

CLINICAL PHARMACOLOGY

Mechanism of Action

Anastrozole is a non-steroidal aromatase inhibitor. The growth of many cancers of the breast is stimulated or maintained by estrogens. In postmenopausal women, estrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens (primarily androstenedione and testosterone) to estrone and estradiol. The suppression of estrogen biosynthesis in peripheral tissues and in the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme.

Pharmacokinetics

Absorption:

Inhibition of aromatase activity is primarily due to Anastrozole, the parent drug. Absorption of Anastrozole is rapid and maximum plasma concentrations typically occur within 2 hours of dosing under fasted conditions. Studies with radiolabeled drug have demonstrated that orally administered Anastrozole is well absorbed into the systemic circulation. Food reduces the rate but not the overall extent of Anastrozole absorption. The mean Cmax of Anastrozole decreased by 16% and the median Tmax was delayed from 2 to 5 hours when Anastrozole was administered 30 minutes after food.

Distribution:

Steady-state plasma levels are approximately 3- to 4-fold higher than levels observed after a single dose of Anastrozole. Plasma concentrations approach steady-state levels at about 7 days of once daily dosing. Anastrozole is 40% bound to plasma proteins in the therapeutic range.

Metabolism:

Metabolism of Anastrozole occurs by N-dealkylation, hydroxylation and glucuronidation. Three metabolites of Anastrozole (triazole, a glucuronide conjugate of hydroxy-anastrozole, and a glucuronide conjugate of Anastrozole itself) have been identified in human plasma and urine. The major circulating metabolite of Anastrozole, triazole, lacks pharmacologic activity.

Excretion:

Eighty-five percent of radiolabeled Anastrozole was recovered in feces and urine. Hepatic metabolism accounts for approximately 85% of Anastrozole elimination. Renal elimination accounts for approximately 10% of total clearance. The mean elimination half-life of Anastrozole is 50 hours.

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 second-line 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 Anastrozole.

DOSAGE AND ADMINISTRATION

The dose of Anacare is one tablet 1 mg 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 postmenonausal women, the optimal duration of therapy is unknown. Patients with Hepatic Impairment: No changes in dose are recommended for patients with mild- to-moderate hepatic impairment. 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.

ADVERSE REACTIONS

Serious adverse reactions with Anastrozole occurring in less than 1 in 10,000 patients, are: 1) skin reactions such as lesions, ulcers, or blisters; 2) allergic reactions with swelling of the face, lips, tongue, and/or throat. This may cause difficulty in swallowing and/or breathing; and 3) changes in blood tests of the liver function, including inflammation of the liver with symptoms that may include a general feeling of not being well, with or without jaundice, liver pain or liver swelling.

Common adverse reactions (occurring with an incidence of >10%) in women taking Anastrozole included: hot flashes, asthenia, arthritis, pain, arthralgia, hypertension, depression, nausea and vomiting, rash, osteoporosis, fractures, back pain, insomnia, pain, headache, bone pain, peripheral edema, increased cough, dyspnea, pharyngitis and lymphedema.

CONTRAINDICATIONS

Pregnancy and Premenopausal Women:

Anastrozole may cause fetal harm when administered to a pregnant woman and offers no clinical benefit to premenopausal women with breast cancer. It is contraindicated in women who are or may become pregnant. There are no adequate and well-controlled studies in pregnant women. If Anastrozole is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus or potential risk for loss of the pregnancy.

Hypersensitivity:

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

PRECAUTIONS

Ischemic Cardiovascular Events:

In women with pre-existing ischemic heart disease, an increased incidence of ischemic cardiovascular events was observed with Anastrozole in the ATAC trial (17% of patients on Anastrozole and 10% of patients on tamoxifen). Risk and benefits of Anastrozole therapy should be considered in patients with pre-existing ischemic heart disease.

Bone Effects:

Results from the ATAC trial bone substudy at 12 and 24 months demonstrated that patients receiving Anastrozole had a mean decrease in both lumbar spine and total hip bone mineral density (BMD) compared to baseline. Patients receiving tamoxifen had a mean increase in both lumbar spine and total hip BMD compared to baseline.

Cholesterol:

During the ATAC trial, more patients receiving Anastrozole were reported to have elevated serum cholesterol compared to patients receiving tamoxifen (9% versus 3.5%, respectively).

DRUG INTERACTIONS

Co-administration of Anastrozole and tamoxifen in breast cancer patients reduced Anastrozole plasma concentration by 27%. Based on clinical and pharmacokinetic results from the ATAC trial, tamoxifen should not be administered with Anastrozole. Estrogen-containing therapies should not be used with Anastrozole as they may diminish its pharmacological action. In a study conducted in 16 male volunteers, Anastrozole did not alter the exposure (as measured by Cmax and AUC) and anticoagulant activity (as measured by prothrombin time, activated partial thromboplastin time, and thrombin time) of both R- and S-warfarin. Based on in vitro and in vivo results, it is unlikely that co-administration of Anastrozole 1 mg will affect other drugs as a result inhibition of cytochrome P450.

Pregnancy: Pregnancy Category X.

Nursing Mothers: It is not known it Anastrozole is excreted in human milk. Because many drugs are excreted in human milk or the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

Geriatric Use: The pharmacokinetics of Anastrozole are not affected by age.

OVERDOSAGE

Clinical trials have 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 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). There is no specific antidote to overdosage and treatment must be symptomatic.

PHARMACEUTICAL INFORMATION

Storage condition: Store below 25° C in a dry place. Keep out of the reach of children.

Packaging: Anacare Tablet: Each box contains 28 tablets in Alu-Alu blister pack.