Anastrozole

Anazole®

1 mg Film-Coated Tablet
Aromatase Inhibitor

FORMULATION
Each film-coated tablet contains:
Anastrozole, USP ..... 1 mg

PRODUCT DESCRIPTION
Round, biconvex smooth, white film-coated tablets, 6 mm +/- 0.2 mm diameter.

CLINICAL PHARMACOLOGY
PHARMACODYNAMICS / MECHANISM OF ACTION
Anastrozole is a highly selective, nonsteroidal aromatase inhibitor. It stops tumor growth and delays disease progression by blocking the conversion of androgens to estrogens. In postmenopausal women, estradiol is produced primarily from the conversion of androstenedione to estrone through the aromatase enzyme complex in peripheral tissues. Aromatase inhibition decreases circulating estrogen, leading to a decreased breast tumor mass or delayed progression of breast tumor growth.

PHARMACOKINETICS
Anastrozole absorption is rapid and maximum plasma concentrations typically occur within two hours of dosing. Food slightly decreases the rate but not the extent of absorption. The small change in the rate of absorption is not expected to result in a clinically significant effect on steady-state plasma concentrations during once a day dosing of anastrozole tablets. Plasma anastrozole steady-state concentrations are attained after 7 once daily doses; steady-state concentrations are 3-4 times higher than concentrations following a single dose. There is no evidence of time or dose-dependency of anastrozole pharmacokinetic parameters. Anastrozole is only 40 % bound to plasma proteins.

Anastrozole is extensively metabolized mainly in the liver (about 85%) by N-dealkylation, hydroxylation, and glucuronidation to inactive metabolites. Less than 10% of the dose is excreted in the urine unchanged within 72 hours of dosing while about 60% of the dose is excreted in urine as metabolites. Anastrozole is eliminated slowly with a plasma elimination half-life of 40 to 50 hours. Triazole, a major metabolite in plasma and urine, does not inhibit aromatase.

The apparent oral clearance of anastrozole in volunteers with stable hepatic cirrhosis or renal impairment was in the range observed in healthy volunteers.

Anastrozole pharmacokinetics is independent of age in postmenopausal women. Pharmacokinetics has not been studied in children.

INDICATIONS
- Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.
- First-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer.
- Treatment of advanced breast cancer in postmenopausal women with disease progression after tamoxifen therapy.

DOSAGE AND ADMINISTRATION
Recommended Dose: Orally, 1 tablet once daily.

- The optimal duration of therapy is unknown for adjuvant treatment of early breast cancer. Anastrozole was administered for 5 years in a clinical trial.
- For treatment of advanced breast cancer, anastrozole therapy should be continued until tumor progression is evident.

Or, as directed by a doctor.

CONTRAINDICATIONS
- Hypersensitivity to anastrozole or any component in the product
- Premenopausal women
- Patients with severe kidney failure
- Patients with moderate to severe liver failure
- Pregnant or breastfeeding women
- Concomitant use of:
  - Selective estrogen receptor modulators (e.g., tamoxifen, raloxifene)
  - Other aromatase inhibitors (e.g., exemestane, formestane, letrozole)
- Not recommended for use in children

WARNINGS AND PRECAUTIONS
- Anastrozole should only be given under the supervision of a physician experienced in the use of anticancer drugs.
- Pregnancy should be ruled out before initiating anastrozole therapy.
- Postmenopausal women receiving anastrozole are at high risk for osteoporosis. Anastrozole has been reported to cause a reduction in bone mineral density (BMD) due to lowering of circulating estrogen concentrations. Patients should undergo screening to determine BMD before initiation of anastrozole and at regular intervals during long-term therapy. Patients with osteoporosis or osteopenia should be monitored carefully and treated as clinically indicated.
- Lifestyle changes such as weight-bearing exercise and dietary supplementation with calcium and vitamin D are advised to reduce the risk of osteoporosis in women taking anastrozole as adjuvant therapy.
- Monitor serum lipoprotein concentrations in patients receiving long-term anastrozole therapy.

MUTAGENICITY AND CARCINOGENICITY
Mutagenicity: Genetic toxicology studies show that anastrozole is not a mutagen or a clastogen.

Carcinogenicity: A two-year rat oncogenicity study showed an increased incidence of hepatic neoplasms and uterine stromal polyps in females and thyroid adenomas in males at the high dose (25 mg/kg/day) only. These changes occurred at a dose which represents 100-fold greater exposure than occurs at human therapeutic doses, and are considered not to be clinically relevant to the treatment of patients with anastrozole.
A two-year mouse oncogenicity study showed induction of benign ovarian tumors and a disturbance in the incidence of lymphoreticular neoplasms (fewer histiocytic sarcomas in females and more deaths as a result of lymphomas). These changes are considered to be mouse-specific effects of aromatase inhibition and not clinically relevant to the treatment of patients with anastrozole.

REPRODUCTIVE TOXICOLOGY
Oral administration of anastrozole to pregnant rats and rabbits caused no teratogenic effects at doses up to 1 and 0.2 mg/kg/day, respectively. Those effects seen (placental enlargement in rats and pregnancy failure in rabbits) were related to the pharmacology of the compound.

Oral administration of anastrozole to female rats produced a high incidence of infertility at 1 mg/kg/day and increased pre-implantation loss at 0.02 mg/kg/day. These effects were related to the pharmacology of the compound and were completely reversed after a 5-week compound withdrawal period.

The survival of litters born to rats given anastrozole at 0.02 mg/kg/day and above (from day 17 of pregnancy to day 22 post-partum) was compromised. These effects were related to the pharmacological effects of the compound on parturition. There were no adverse effects on behavior of reproductive performance of the first generation offspring attributable to maternal treatment with anastrozole.

EFFECTS ON ABILITY TO DRIVE OR USE MACHINES
Anastrozole is unlikely to impair the ability of patients to drive or operate machinery. However, asthenia and somnolence have been reported with the use of anastrozole. Caution should be observed when driving or operating machinery.

DRUG INTERACTIONS
- Selective estrogen receptor modulators (e.g., tamoxifen, raloxifene) and aromatase inhibitors (e.g., anastrozole, letrozole) should not be taken concomitantly.
- Concomitant use with estrogens may diminish the action of anastrozole.
- Anastrozole may inhibit the *in vitro* metabolic reactions catalyzed by cytochrome P-450 isoenzymes 1A2, 2C8/9, and 3A4 but only at high concentrations.
- No clinically significant interaction is seen when anastrozole is administered concurrently with bisphosphonates.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
PREGNANCY AND LACTATION
Anastrozole is contraindicated in pregnant women since it may cause harm to the fetus. Patients who are pregnant or who become pregnant should be informed of the potential hazard to the fetus and the potential risk for loss of the pregnancy.

It is not known whether anastrozole is distributed in breastmilk. However, because of the possibility of the drug being excreted in breastmilk, it should not be administered to breastfeeding women.

GERIATRICS
No dosage adjustment is necessary in elderly patients receiving anastrozole. There is no reported evidence of altered pharmacokinetics in women older than 80 years old.

INFANTS AND CHILDREN
Safety and effectiveness of anastrozole in pediatric patients younger than 18 years old has not been established. Anastrozole is not recommended for use in children.

HEPATIC AND RENAL IMPAIRMENT
Dosage adjustment is not required in patients with mild to moderate renal and hepatic impairment. However, patients with hepatic disease resulting in severe hepatic impairment should be carefully monitored for adverse effects since almost 85% of anastrozole elimination occurs in the liver.

ADVERSE EFFECTS / UNDESIRABLE EFFECTS
Anastrozole has been shown to be generally well-tolerated in patients with advanced breast cancer in clinical trials.

Cardiovascular Effects: Ischemic cerebrovascular events and ischemic cardiovascular disease; angina pectoris and myocardial infarction have been reported with anastrozole use as adjuvant therapy. Thromboembolic diseases such as venous thrombosis (including pulmonary embolus, thrombophlebitis, and retinal vein thrombosis), coronary and/or cerebral thrombosis (including myocardial infarction, myocardial ischemia, angina pectoris, cerebrovascular accident, cerebral ischemia, and cerebral infarct) have been reported in patients receiving anastrozole as first-line therapy.
Other effects may include hot flushes, increased serum cholesterol, vasodilation, hypertension, lymphedema, and peripheral edema.

Genitourinary Effects: Adjuvant therapy with anastrozole may cause vaginal bleeding, vaginal discharge and vulvovaginitis. Endometrial cancer was also reported.
First-line or second-line therapy with anastrozole may cause adverse effects such as pelvic pain, vaginal bleeding and vaginal dryness. Breast pain, urinary tract infection and leukorrhea were also reported.

Musculoskeletal Effects: Patients receiving anastrozole are at high risk for osteoporosis since the drug may cause a reduction in bone mineral density.
Joint symptoms including arthritis, arthrosis, and arthralgia and fractures of the spine, hip, and wrist have been reported with anastrozole use.
Other effects may include bone pain, myalgia, pathologic fracture, back pain, and neck pain. Hands, knees, hips, lower back, or shoulders may experience joint pains. Stiffness, particularly in the morning has also been reported.

Gastrointestinal Effects: Nausea and vomiting; dyspepsia, diarrhea, abdominal pain, constipation, and anorexia and unspecified GI disorder.

Respiratory Effects: Pharyngitis, dyspnea, sinusitis, bronchitis, rhinitis, and increased cough.

CNS Effects: CNS effects have been reported including mood disturbance, depression, insomnia, anxiety, headache, dizziness, paresthesia, somnolence, confusion, nervousness, and hypertonia.

Dermatologic Effects: Rash, sweating, hair thinning and pruritus have been reported with anastrozole therapy. Mucocutaneous disorders, including erythema multiforme and Stevens-Johnson syndrome have also been reported rarely.

Hepatic Effects: Increased serum concentrations of γ-glutamyltransferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase were reported.

Hematologic Effects: Anemia and leukopenia.

Sensitivity Reactions: Rare reports of systemic allergic reactions including angioedema, urticaria, and anaphylaxis in patients receiving anastrozole.

Others: Weight loss, weight gain, cataracts, asthenia, nonspecific pain, chest pain (nonspecific), flu syndrome, accidental injury, lethargy, fever, and malaise.

OVERDOSAGE AND MANAGEMENT
There is limited clinical experience of anastrozole overdose. Single dose of up to 60 mg in healthy males and daily multiple doses of 10 mg in postmenopausal women with advanced breast cancer have been administered without evidence of toxicity.

Studies in rats and dogs demonstrated lethality after single doses of anastrozole greater than 100 mg/kg (about 800 times the recommended human dose on a mg/m^2 basis) and 45 mg/kg, respectively. Severe irritation of the stomach, including necrosis, gastritis, ulceration, and hemorrhage were manifested.

Overdosage of anastrozole may require symptomatic and supportive therapy. Consideration should be given to the possibility that multiple agents may have been taken. Frequent monitoring of vital signs and close observation of the patient is necessary. Vomiting may be induced in conscious patients. Dialysis may also be helpful since anastrozole is not highly protein bound.

STORAGE CONDITION
Store at temperatures not exceeding 30°C.

AVAILABILITY
Alu/ PVC Blister Pack of 14's. Box of 28 film - coated tablets . - DR-XY40800

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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Manufactured by Laboratorios Richmond S.A.C.I.F.
Street 3 N°519 Pilar Industrial Park
of the Province of Buenos Aires
Republica Argentina
Imported and Distributed by
UNILAB, Inc.
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

Date of First Authorization: April 2012
Date of Revision: August 2018

BIO154625IN02 *Reg. IPOPHIL

041636-03