ANASTROZOLE- anastrozole tablet
Northwind Pharmaceuticals, LLC

Anastrozole

INDICATIONS & USAGE

1.1 Adjuvant Treatment

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

1.2 First-Line Treatment

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

1.3 Second-Line Treatment

Anastrozole tablets are 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 anastrozole tablets.

DOSAGE & ADMINISTRATION

2.1 Recommended Dose

The dose of anastrozole tablet is one 1 mg tablet taken once a day. For patients with advanced breast cancer, anastrozole tablets should be continued until tumor progression. Anastrozole tablets can be taken with or without food.

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 [see Clinical Studies (14.1)].

No dosage adjustment is necessary for patients with renal impairment or for elderly patients [see Use in Specific Populations (8.6)].

2.2 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 [see Use in Specific Populations (8.7)].

DOSAGE FORMS & STRENGTHS

The tablets are white to off-white, round biconvex, film coated tablets, with “AHI” debossing on one side and plain on other side.

CONTRAINDICATIONS

4.1 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. Anastrozole is contraindicated in women who are or may become pregnant. 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 taking this

drug, the patient should be apprised of the potential hazard to a fetus or potential risk for loss of the pregnancy [see Use in Specific Populations (8.1)].

4.2 Hypersensitivity

Anastrozole is contraindicated in any patient who has shown a hypersensitivity reaction to the drug or to any of the excipients. Observed reactions include anaphylaxis, angioedema, and urticaria [see Adverse Reactions (6.2)].

WARNINGS AND PRECAUTIONS

5.1 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). Consider risk and benefits of anastrozole therapy in patients with pre-existing ischemic heart disease [see Adverse Reactions (6.1)].

5.2 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. Consider bone mineral density monitoring in patients treated with anastrozole [see Adverse Reactions (6.1)] .

5.3 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) [see Adverse Reactions (6.1)].

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 [see Adverse Reactions (6.2)].

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, headache, bone pain, peripheral edema, increased cough, dyspnea, pharyngitis and lymphedema.

In the ATAC trial, the most common reported adverse reaction (>0.1%) leading to discontinuation of therapy for both treatment groups was hot flashes, although there were fewer patients who discontinued therapy as a result of hot flashes in the anastrozole group.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience

Adjuvant Therapy

Adverse reaction data for adjuvant therapy are based on the ATAC trial [see Clinical Studies (14.1)]. The median duration of adjuvant treatment for safety evaluation was 59.8 months and 59.6 months for

patients receiving anastrozole 1 mg and tamoxifen 20 mg, respectively. For the list of adverse events please see the manufacturer's drug information.

PLEASE REVIEW THE MANUFACTURER'S COMPLETE DRUG INFORMATION AT THE FDA SITE:

http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=03586c40-eb32-45c5-beb7-6762a6b78790

Ischemic Cardiovascular Events

Between treatment arms in the overall population of 6186 patients, there was no statistical difference in ischemic cardiovascular events (4% anastrozole vs. 3% tamoxifen). In the overall population, angina pectoris was reported in 71/3092 (2.3%) patients in the anastrozole arm and 51/3094 (1.6%) patients in the tamoxifen arm; myocardial infarction was reported in 37/3092 (1.2%) patients in the anastrozole arm and 34/3094 (1.1%) patients in the tamoxifen arm.

In women with pre-existing ischemic heart disease 465/6186 (7.5%), the incidence of ischemic cardiovascular events was 17% in patients on anastrozole and 10% in patients on tamoxifen. In this patient population, angina pectoris was reported in 25/216 (11.6%) patients receiving anastrozole and 13/249 (5.2%) patients receiving tamoxifen; myocardial infarction was reported in 2/216 (0.9%) patients receiving anastrozole and 8/249 (3.2%) patients receiving tamoxifen.

Bone Mineral Density Findings

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.

Because anastrozole lowers circulating estrogen levels it may cause a reduction in bone mineral density.

A post-marketing trial assessed the combined effects of anastrozole and the bisphosphonate risedronate on changes from baseline in BMD and markers of bone resorption and formation in postmenopausal women with hormone receptor-positive early breast cancer. All patients received calcium and vitamin D supplementation. At 12 months, small reductions in lumbar spine bone mineral density were noted in patients not receiving bisphosphonates. Bisphosphonate treatment preserved bone density in most patients at risk of fracture.

Postmenopausal women with early breast cancer scheduled to be treated with anastrozole should have their bone status managed according to treatment guidelines already available for postmenopausal women at similar risk of fragility fracture.

Cholesterol

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

A post-marketing trial also evaluated any potential effects of anastrozole on lipid profile. In the primary analysis population for lipids (anastrozole alone), there was no clinically significant change in LDL-C from baseline to 12 months and HDL-C from baseline to 12 months.

In secondary population for lipids (anastrozole+risedronate), there also was no clinically significant change in LDL-C and HDL-C from baseline to 12 months.

In both populations for lipids, there was no clinically significant difference in total cholesterol (TC) or serum triglycerides (TG) at 12 months compared with baseline.

In this trial, treatment for 12 months with anastrozole alone had a neutral effect on lipid profile. Combination treatment with anastrozole and risedronate also had a neutral effect on lipid profile.

The trial provides evidence that postmenopausal women with early breast cancer scheduled to be treated with anastrozole should be managed using the current National Cholesterol Education Program guidelines for cardiovascular risk-based management of individual patients with LDL elevations.

Other Adverse Reactions

Patients receiving anastrozole had an increase in joint disorders (including arthritis, arthrosis and arthralgia) compared with patients receiving tamoxifen. Patients receiving anastrozole had an increase in the incidence of all fractures (specifically fractures of spine, hip and wrist) [315 (10%)] compared with patients receiving tamoxifen [209 (7%)].

Patients receiving anastrozole had a higher incidence of carpal tunnel syndrome [78 (2.5%)] compared with patients receiving tamoxifen [22 (0.7%)].

Vaginal bleeding occurred more frequently in the tamoxifen-treated patients versus the anastrozole - treated patients 317 (10%) versus 167 (5%), respectively.

Patients receiving anastrozole had a lower incidence of hot flashes, vaginal bleeding, vaginal discharge, endometrial cancer, venous thromboembolic events and ischemic cerebrovascular events compared with patients receiving tamoxifen.

10-year median follow-up Safety Results from the ATAC Trial

Results are consistent with the previous analyses.
Serious adverse reactions were similar between anastrozole (50%) and tamoxifen (51%).
Cardiovascular events were consistent with the known safety profiles of anastrozole and tamoxifen.
The cumulative incidences of all first fractures (both serious and non-serious, occurring either during or after treatment) was higher in the anastrozole group (15%) compared to the tamoxifen group (11%). This increased first fracture rate during treatment did not continue in the post-treatment follow-up period.
The cumulative incidence of new primary cancers was similar in the anastrozole group (13.7%) compared to the tamoxifen group (13.9%). Consistent with the previous analyses, endometrial cancer was higher in the tamoxifen group (0.8%) compared to the anastrozole group (0.2%).
The overall number of deaths (during or off-trial treatment) was similar between the treatment groups. There were more deaths related to breast cancer in the tamoxifen than in the anastrozole treatment group.

PLEASE REVIEW THE MANUFACTURER'S COMPLETE DRUG INFORMATION THAT INCLUDES FIRST-LINE THERAPY, SECOND-LINE THERAPY AND ALL OTHER IMPORTANT INFORMATION AT THE FDA SITE:

http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=03586c40-eb32-45c5-beb7-6762a6b78790

6.2 Post-Marketing Experience

These adverse reactions are reported voluntarily from a population of uncertain size. Therefore, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. The following have been reported in post-approval use of anastrozole:

Hepatobiliary events including increases in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-GT, and bilirubin; hepatitis

Rash including cases of mucocutaneous disorders such as erythema multiforme and Stevens-Johnson syndrome.

Cases of allergic reactions including angioedema, urticaria and anaphylaxis. [see Contraindications (4.2)]

Myalgia, trigger finger and hypercalcemia (with or without an increase in parathyroid hormone)

DRUG INTERACTIONS

7.1 Tamoxifen

Co-administration of anastrozole and tamoxifen in breast cancer patients reduced anastrozole plasma concentration by 27%. However, the co-administration of anastrozole and tamoxifen did not affect the pharmacokinetics of tamoxifen or N-desmethyltamoxifen. 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. [see Clinical Studies (14.1)] . Based on clinical and pharmacokinetic results from the ATAC trial, tamoxifen should not be administered with anastrozole.

7.2 Estrogen

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

7.3 Warfarin

In a study conducted in 16 male volunteers, anastrozole did not alter the exposure (as measured by C max and AUC), and anticoagulant activity (as measured by prothrombin time, activated partial thromboplastin time, and thrombin time) of both R- and S-warfarin.

7.4 Cytochrome P450

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 of inhibition of cytochrome P450 [see Clinical Pharmacology (12.3)].

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

PREGNANCY CATEGORY X [see Contraindications (4.1)]

Anastrozole may cause fetal harm when administered to a pregnant woman and offers no clinical benefit to premenopausal women with breast cancer. Anastrozole is contraindicated in women who are or may become pregnant. In animal studies, anastrozole caused pregnancy failure, increased pregnancy loss, and signs of delayed fetal development. There are no studies of anastrozole use in pregnant women. If anastrozole 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 and potential risk for pregnancy loss.

In animal reproduction studies, pregnant rats and rabbits received anastrozole during organogenesis at doses equal to or greater than 1 (rats) and 1/3 (rabbits) the recommended human dose on a mg/m 2 basis. In both species, anastrozole crossed the placenta, and there was increased pregnancy loss (increased pre- and/or post-implantation loss, increased resorption, and decreased numbers of live fetuses). In rats, these effects were dose related, and placental weights were significantly increased. Fetotoxicity, including delayed fetal development (i.e., incomplete ossification and depressed fetal body weights), occurred in rats at anastrozole doses that produced peak plasma levels 19 times higher than serum levels in humans at the therapeutic dose (AUC 0-24hr 9 times higher). In rabbits, anastrozole caused pregnancy failure at doses equal to or greater than 16 times the recommended human dose on a mg/m 2 basis [see Animal Toxicology and/or Pharmacology (13.2)].

8.3 Nursing Mothers

It is not known if anastrozole is excreted in human milk. Because many drugs are excreted in human milk and because of the tumorigenicity shown for anastrozole in animal studies, 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.

8.4 Pediatric Use

Clinical studies in pediatric patients included a placebo-controlled trial in pubertal boys of adolescent age with gynecomastia and a single-arm trial in girls with McCune-Albright Syndrome and progressive precocious puberty. The efficacy of anastrozole in the treatment of pubertal gynecomastia in adolescent boys and in the treatment of precocious puberty in girls with McCune-Albright Syndrome has not been demonstrated.

Gynecomastia Study

A randomized, double-blind, placebo-controlled, multi-center study enrolled 80 boys with pubertal gynecomastia aged 11 to 18 years. Patients were randomized to a daily regimen of either anastrozole 1 mg or placebo. After 6 months of treatment there was no statistically significant difference in the percentage of patients who experienced a ≥50% reduction in gynecomastia (primary efficacy analysis). Secondary efficacy analyses (absolute change in breast volume, the percentage of patients who had any reduction in the calculated volume of gynecomastia, breast pain resolution) were consistent with the primary efficacy analysis. Serum estradiol concentrations at Month 6 of treatment were reduced by 15.4% in the anastrozole group and 4.5% in the placebo group.

Adverse reactions that were assessed as treatment-related by the investigators occurred in 16.3% of the anastrozole-treated patients and 8.1% of the placebo-treated patients with the most frequent being acne (7% anastrozole and 2.7% placebo) and headache (7% anastrozole and 0% placebo); all other adverse reactions showed small differences between treatment groups. One patient treated with anastrozole discontinued the trial because of testicular enlargement. The mean baseline-subtracted change in testicular volume after 6 months of treatment was + 6.6 ± 7.9 cm 3 in the anastrozole-treated patients and + 5.2 ± 8.0 cm 3 in the placebo group.

McCune-Albright Syndrome Study

A multi-center, single-arm, open-label study was conducted in 28 girls with McCune-Albright Syndrome and progressive precocious puberty aged 2 to <10 years. All patients received a 1 mg daily dose of anastrozole. The trial duration was 12 months. Patients were enrolled on the basis of a diagnosis of typical (27/28) or atypical (1/27) McCune-Albright Syndrome, precocious puberty, history of vaginal bleeding, and/or advanced bone age. Patients' baseline characteristics included the following: a mean chronological age of 5.9 ± 2.0 years, a mean bone age of 8.6 ± 2.6 years, a mean growth rate of 7.9 ± 2.9 cm/year and a mean Tanner stage for breast of 2.7 ± 0.81. Compared to pre-treatment data there were no on-treatment statistically significant reductions in the frequency of vaginal bleeding days, or in the rate of increase of bone age (defined as a ratio between the change in bone age over the change of chronological age). There were no clinically significant changes in Tanner staging,mean ovarian volume, mean uterine volume and mean predicted adult height. A small but statistically significant reduction of growth rate from 7.9 ± 2.9 cm/year to 6.5 ± 2.8 cm/year was observed but the absence of a control group precludes attribution of this effect to treatment or to other confounding factors such as variations in endogenous estrogen levels commonly seen in McCune-Albright Syndrome patients.

Five patients (18%) experienced adverse reactions that were considered possibly related to anastrozole. These were nausea, acne, pain in an extremity, increased alanine transaminase and aspartate transaminase, and allergic dermatitis.

Pharmacokinetics in Pediatric Patients

Following 1 mg once daily multiple administration in pediatric patients, the mean time to reach the maximum anastrozole concentration was 1 hr. The mean (range) disposition parameters of anastrozole in pediatric patients were described by a CL/F of 1.54 L/h (0.77 to 4.53 L/h) and V/F of 98.4 L (50.7 to 330.0 L). The terminal elimination half-life was 46.8 h, which was similar to that observed in postmenopausal women treated with anastrozole for breast cancer. Based on a population pharmacokinetic analysis, the pharmacokinetics of anastrozole was similar in boys with pubertal gynecomastia and girls with McCune- Albright Syndrome.

8.5 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 study, 45% of patients were 65 years of age or older. The efficacy of anastrozole compared to tamoxifen in patients who were 65 years or older (N=1413 for anastrozole and N=1410 for tamoxifen, the hazard ratio for disease-free survival was 0.93 [95% CI: 0.80, 1.08]) was less than efficacy observed in patients who were less than 65 years of age (N=1712 for anastrozole and N=1706 for tamoxifen, the hazard ratio for disease-free survival was 0.79 [95% CI: 0.67, 0.94]).

The pharmacokinetics of anastrozole is not affected by age.

8.6 Renal Impairment

Since only about 10% of anastrozole is excreted unchanged in the urine, the renal impairment does not influence the total body clearance. Dosage adjustment in patients with renal impairment is not necessary [see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment

The plasma anastrozole concentrations in the subjects with hepatic cirrhosis were within the range of concentrations seen in normal subjects across all clinical trials. Therefore, dosage adjustment is also not necessary in patients with stable hepatic cirrhosis. Anastrozole has not been studied in patients with severe hepatic impairment [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

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 tolerated. A single dose of anastrozole that results in life-threatening symptoms has not been established. 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 anastrozole is not highly protein bound. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

DESCRIPTION

Anastrozole 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-1-ylmethyl). Its molecular formula is C 17H 19N 5.

Anastrozole 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.

Each tablet contains as inactive ingredients: lactose monohydrate, magnesium stearate, hypromellose, macrogol, povidone, sodium starch glycolate, and titanium dioxide.

CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

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

12.2 Pharmacodynamics

Effect on Estradiol

Mean serum concentrations of estradiol were evaluated in multiple daily dosing trials with 0.5, 1, 3, 5, and 10 mg 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 (3.7 pmol/L). The recommended daily dose, anastrozole 1 mg, reduced estradiol by approximately 70% within 24 hours and 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 with anastrozole 1 mg.

The effect of anastrozole in premenopausal women with early or advanced breast cancer has not been studied. Because aromatization of adrenal androgens is not a significant source of estradiol in premenopausal women, anastrozole would not be expected to lower estradiol levels in premenopausal women.

Effect 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 mineralocorticoid replacement therapy is necessary with anastrozole.

Other Endocrine Effects

In multiple daily dosing trials with 5 and 10 mg, thyroid stimulating hormone (TSH) was 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.

12.3 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 C max of anastrozole decreased by 16% and the median T max was delayed from 2 to 5 hours when anastrozole was administered 30 minutes after food. The pharmacokinetics of anastrozole are linear over the dose range of 1 to 20 mg, and do not change with repeated dosing. The pharmacokinetics of anastrozole were similar in patients and healthy volunteers.

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.

Anastrozole inhibited reactions catalyzed by cytochrome P450 1A2, 2C8/9, and 3A4 in vitro with Ki values which were approximately 30 times higher than the mean steady-state Cmax values observed following a 1 mg daily dose. Anastrozole had no inhibitory effect on reactions catalyzed by cytochrome P450 2A6 or 2D6 in vitro. Administration of a single 30 mg/kg or multiple 10 mg/kg doses of anastrozole to healthy subjects had no effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites.

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.

Effect of Gender and Age

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.

Effect of Race

Estradiol and estrone sulfate serum 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 30.4 ng/mL, respectively.

Effect of Renal Impairment

Anastrozole pharmacokinetics have been investigated in subjects with renal impairment. 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. Total clearance was only reduced 10%. No dosage adjustment is needed for renal impairment. [see Dosage and Administration (2.1) and Use in Specific Populations (8.6)]

Effect of Hepatic Impairment

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, these plasma concentrations were still with the range of values observed in normal subjects. The effect of severe hepatic impairment was not studied. No dose adjustment is necessary for stable hepatic cirrhosis. [see Dosage and Administration (2.2) and Use in Specific Populations (8.7)]

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 0-24 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.

Anastrozole 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).

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 0-24 hr found in postmenopausal volunteers at the recommended dose). Pre-implantation loss of ova or fetus was increased at doses equal to or greater than 0.02 mg/kg/day (about one-fifth the recommended human dose on a mg/m 2 basis). Recovery of fertility was observed following a 5-week non-dosing period which followed 3 weeks of dosing. It is not known whether these effects observed in female rats are indicative of impaired fertility in humans.

Multiple-dose studies in rats administered anastrozole for 6 months at doses equal to or greater than 1 mg/kg/day (which produced plasma anastrozole C ssmax and AUC 0-24 hr that were 19 and 9 times higher than the respective values found in postmenopausal volunteers at the recommended dose) resulted in hypertrophy of the ovaries and the presence of follicular cysts. In addition, hyperplastic uteri were observed in 6-month studies in female dogs administered doses equal to or greater than 1 mg/kg/day (which produced plasma anastrozole C ssmax and AUC 0-24 hr that were 22 times and 16 times higher than the respective values found in postmenopausal women at the recommended dose). It is not known whether these effects on the reproductive organs of animals are associated with impaired fertility in premenopausal women.

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology

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 C ssmax and AUC 0-24 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/m 2 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).

PATIENT COUNSELING INFORMATION

“See FDA approved patient labeling (Patient Information).”

17.1 Pregnancy

Patients should be advised that anastrozole may cause fetal harm. They should also be advised that anastrozole is not for use in premenopausal women; therefore, if they become pregnant, they should stop taking anastrozole tablets and immediately contact their doctor.

17.2 Allergic (Hypersensitivity) Reactions

Patients should be informed of the possibility of serious allergic reactions with swelling of the face, lips, tongue and/or throat (angioedema) which may cause difficulty in swallowing and/or breathing and to seek medical attention immediately.

17.3 Ischemic Cardiovascular Events

Patients with pre-existing ischemic heart disease should be informed that an increased incidence of cardiovascular events has been observed with anastrozole use compared to tamoxifen use. If patients have new or worsening chest pain or shortness of breath they should seek medical attention immediately.

17.4 Bone Effects

Patients should be informed that anastrozole lowers the level of estrogen. This may lead to a loss of the mineral content of bones, which might decrease bone strength. A possible consequence of decreased mineral content of bones is an increase in the risk of fractures.

17.5 Cholesterol

Patients should be informed that an increased level of cholesterol might be seen while receiving anastrozole.

17.6 Tickling, Tingling or Numbness

Patients should be informed that if they experience tickling, tingling, or numbness they should notify their health care provider.

17.7 Tamoxifen

Patients should be advised not to take anastrozole with tamoxifen.

17.8 Missed Doses

Inform patients that if they miss a dose, take it as soon as they remember. If it is almost time for their next dose, skip the missed dose and take the next regularly scheduled dose. Patients should not take two doses at the same time.

PATIENT PACKAGE INSERT

Patient Information

Anastrozole Tablets
(an as' troe zole)

What is the most important information I should know about anastrozole tablet? Anastrozole tablets may cause serious side effects including:

heart disease. Women with early breast cancer, who have a history of blockage in their heart arteries (ischemic heart disease) and who take anastrozole tablets, may have an increase in symptoms of decreased blood flow to their heart compared to similar women who take tamoxifen.

Get medical help right away if you have new or worsening chest pain or shortness of breath during treatment with anastrozole tablets.

What is anastrozole tablet?

Anastrozole tablet is a prescription medicine used in women after menopause (“the change of life”) for:

treatment of early breast cancer
after surgery
in women whose breast cancer is hormone receptor-positive

the first treatment of breast cancer that has spread to nearby tissue or lymph nodes (locally advanced) or has spread to other parts of the body (metastatic), in women whose breast cancer is hormone receptor-positive or the hormone receptors are not known

treatment of advanced breast cancer, if the cancer has grown, or the disease has spread after tamoxifen therapy.

Anastrozole tablet does not work in women with breast cancer who have not gone through menopause (premenopausal women).

Who should not take anastrozole tablets?

Do not take anastrozole tablet if you:

are pregnant or able to become pregnant. Anastrozole tablet may harm your unborn baby. If you become pregnant while taking anastrozole tablet, tell your doctor right away.

have not gone through menopause (are premenopausal).
have had a severe allergic reaction to anastrozole or any of the ingredients in anastrozole tablets. See the end of this leaflet for a complete list of ingredients in anastrozole tablets. Symptoms of a severe allergic reaction to
anastrozole tablets include: swelling of the face, lips, tongue or throat, trouble breathing or swallowing, hives and itching.

What should I tell my doctor before taking anastrozole tablets?

Before you take anastrozole tablets, tell your doctor if you:

have not gone through menopause. Talk to your doctor if you are not sure.
have or had a heart problem
have been told you have bone thinning or weakness (osteoporosis)
have high cholesterol
have any other medical conditions

are pregnant or plan to become pregnant. Anastrozole tablet may harm your unborn baby. See “Who should not take anastrozole tablets?”
are breastfeeding or plan to breastfeed. It is not known if anastrozole passes into breast milk. You and your doctor should decide if you will take anastrozole tablets or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your doctor if you take:

Tamoxifen. You should not take anastrozole tablets if you take tamoxifen. Taking anastrozole tablets with tamoxifen may lower the amount of anastrozole in your blood and may cause anastrozole tablets not to work as well.

Medicines that contain estrogen. Anastrozole tablet may not work if taken with any of these medicines:
hormone replacement therapy
birth control pills
estrogen creams
vaginal rings
vaginal suppositories

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take anastrozole tablets?

Take anastrozole tablets exactly as your doctor tells you to take it. Continue taking anastrozole tablets until your doctor tells you to stop.

Anastrozole tablets can be taken with or without food.

If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Take your next regularly scheduled dose. Do not take two doses at the same time.
If you take too much anastrozole tablets, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of anastrozole tablets?

Anastrozole tablets may cause serious side effects including:

See " What is the most important information I should know about anastrozole tablet ?"
bone thinning or weakness (osteoporosis). Anastrozole lowers estrogen in your body, which may cause your bones to become thinner and weaker. This may increase your risk of fractures, especially of your spine, hip and wrist. Your doctor may order a bone mineral density test before you start and during treatment with anastrozole tablets to check you for bone changes.
increased blood cholesterol (fat in the blood). Your doctor may do blood tests to check your cholesterol while you are taking anastrozole tablets.
skin reactions. Stop taking anastrozole tablets and call your doctor right away if you get any skin lesions, ulcers, or blisters.
severe allergic reactions. Get medical help right away if you get:

swelling of your face, lips, tongue, or throat.

trouble swallowing or breathing

liver problems. Anastrozole can cause inflammation of your liver and changes in liver function blood tests. Your doctor may check you for this.
Stop taking anastrozole tablets and call your doctor right away if you have any of these signs or symptoms of a liver problem:

a general feeling of not being well

yellowing of your skin or whites of your eyes

pain on the right side of your stomach-area (abdomen)

Common side effects in women taking anastrozole tablets include:

hot flashes

weakness
joint aches
joint pain, stiffness or swelling (arthritis)

pain

sore throat

high blood pressure

depression

nausea and vomiting

rash

back pain

sleep problems

bone pain

headache

swelling of your legs, ankles, or feet

increased cough

shortness of breath

build up of lymph fluid in the tissues of your affected arm (lymphedema)

Anastrozole tablets may also cause you to have tickling, tingling or numbness of your skin.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of anastrozole tablets. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store anastrozole tablets?

Store anastrozole tablets at room temperature between 68°F to 77°F (20°C to 25°C).

Keep anastrozole tablets and all medicines out of the reach of children.

General information about the safe and effective use of anastrozole tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not take anastrozole tablets for a condition for which it was not prescribed. Do not give anastrozole tablets to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about anastrozole tablets that is written for health professionals.

What are the ingredients in anastrozole tablets?

Active ingredient: anastrozole

Inactive ingredients: lactose monohydrate, magnesium stearate, hypromellose, macrogol, povidone, sodium starch glycolate, and titanium dioxide.

This Patient Information has been approved by the U.S. Food and Drug Administration.

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC: 51655-638-53

MFG: 16729-035-15

Anastrozole 1MG

10 Tablets

Rx Only

Lot#

Exp. Date:

Each tablet contains: Anastrozole USP 1mg

Dosage: See prescriber's instructions

Store between 68-77 degrees F. Protect from excessive heat, light and humidity.

Keep out of the reach of children.

Medication guide is found at www.fda.gov/drugs/drugsafety/ucm085729

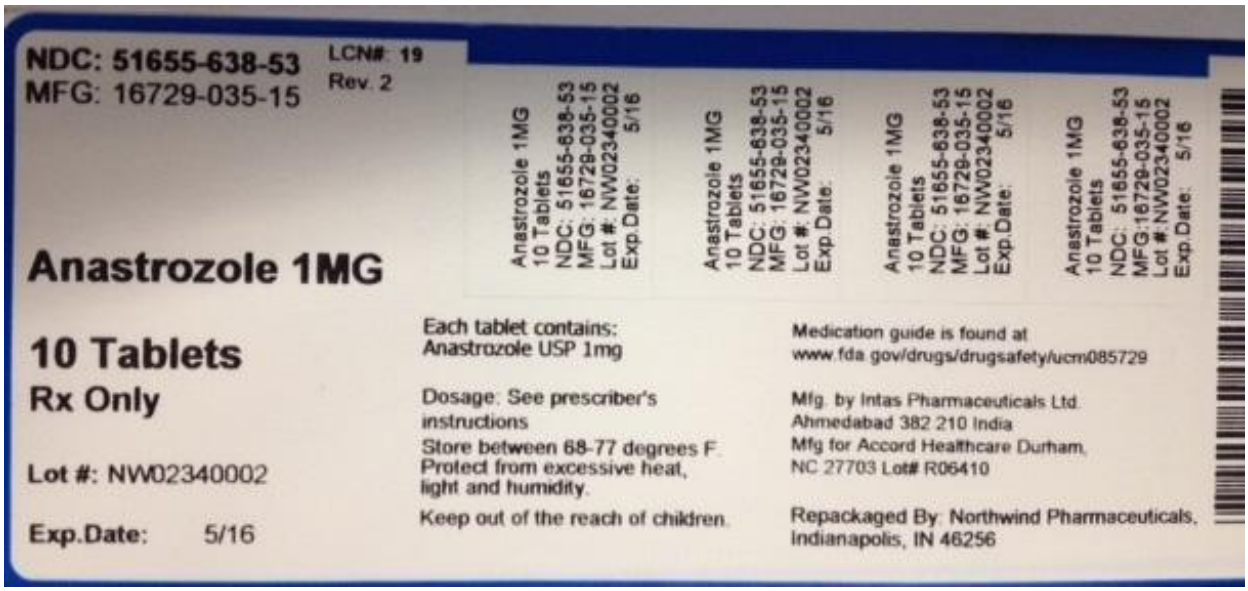
Manufactured By:

Intas Pharmaceuticals Limited, Ahmedabad – 382 210. India.

Manufactured For:

Accord Healthcare, Inc., Durham, NC 27703

Repackaged by Northwind Pharmaceuticals, Indianapolis, IN 46256



ANASTROZOLE

anastrozole tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:51655-638(NDC:16729-035)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ANASTROZOLE (UNII: 2Z07MYW1AZ) (ANASTROZOLE - UNII:2Z07MYW1AZ)	ANASTROZOLE	1 mg

Product Characteristics			
Color	white	**Score**	no score
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	AHI
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:51655-638-53	10 in 1 BOTTLE, DISPENSING		

Marketing Information			
Marketing Category	**Application Number or Monograph Citation**	**Marketing Start Date**	**Marketing End Date**
ANDA	ANDA090568	11/07/2014	

Labeler - Northwind Pharmaceuticals, LLC (036986393)

Registrant - Northwind Pharmaceuticals, LLC (036986393)

Establishment

Name	Address	ID/FEI	Business Operations
Northwind Pharmaceuticals, LLC		036986393	repack(51655-638)

Revised: 11/2014 Northwind Pharmaceuticals, LLC