



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use anastrozole safely and effectively. See full prescribing information for anastrozole.

Anastrozole tablet for oral use

Initial U.S. Approval: 1995

INDICATIONS AND USAGE

Anastrozole is an aromatase inhibitor indicated for:

- Adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer (1.1)
First-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor unknown locally advanced or metastatic breast cancer (1.2)
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 (1.3)

DOSAGE AND ADMINISTRATION

One 1 mg tablet taken once daily (2.1)

DOSAGE FORMS AND STRENGTHS

1 mg tablets (3)

CONTRAINDICATIONS

- Women of premenopausal endocrine status, including pregnant women (4.1, 8.1)
Patients with demonstrated hypersensitivity to anastrozole or any excipient (4.2)

WARNINGS AND PRECAUTIONS

- In women with pre-existing ischemic heart disease, an increased incidence of ischemic cardiovascular events occurred with anastrozole use compared to tamoxifen use. Consider risks and benefits. (5.1, 6.1)
Decreases in bone mineral density may occur. Consider bone mineral density monitoring. (5.2, 6.1)
Increases in total cholesterol may occur. Consider cholesterol monitoring. (5.3, 6.1)

ADVERSE REACTIONS

In the early breast cancer (ATAC) study, the most common (occurring with an incidence of >10%) side effects occurring in women taking anastrozole included: hot flashes, asthenia, arthritis, pain, arthralgia, pharyngitis, hypertension, depression, nausea and vomiting, rash, osteoporosis, fractures, back pain, insomnia, headache, peripheral edema and lymphedema, regardless of causality. (6.1)

In the advanced breast cancer studies, the most common (occurring with an incidence of >10%) side effects occurring in women taking anastrozole included: hot flashes, nausea, asthenia, pain, headache, back pain, bone pain, increased cough, dyspnea, pharyngitis and peripheral edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Zydus Pharmaceuticals (USA) Inc. at 1-877-993-8779 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Tamoxifen: Do not use in combination with anastrozole. No additional benefit seen over tamoxifen monotherapy. (7.1, 14.1).
Estrogen-containing products: Combination use may diminish activity of anastrozole (7.2).

USE IN SPECIFIC POPULATIONS

- Pediatric patients: Efficacy has not been demonstrated for pubertal boys of age with gynecomastia or girls with McCune-Albright Syndrome and progressive precocious puberty. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Patient Labeling.

Revised: 05/2011

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Table with 4 columns: Anastrozole Tablets, Tamoxifen, Odds-ratio, 95% CI. Rows include Cataracts, Vaginal Bleeding, Ischemic Cardiovascular Disease, Vaginal Discharge, Venous Thromboembolic events, Deep Venous Thrombotic Events, Ischemic Cerebrovascular Event, Endometrial Cancer.

Patients with multiple events in the same category are counted only once in that category. Refers to joint symptoms, including joint disorder, arthritis, arthrosis and arthralgia. Percentages calculated based upon the numbers of patients with an intact uterus at baseline.

Ischemic Cardiovascular Events: Between treatment arms in the overall population of 6186 patients, there was no statistical difference in ischemic cardiovascular events (4% anastrozole tablets vs. 3% tamoxifen).

In the overall population, angina pectoris was reported in 71/3092 (2.3%) patients in the anastrozole tablets arm and 51/3094 (1.6%) patients in the tamoxifen arm; myocardial infarction was reported in 37/3092 (1.2%) patients in the anastrozole tablets 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 tablets and 10% in patients on tamoxifen. In this patient population, angina pectoris was reported in 25/216 (11.6%) patients receiving anastrozole tablets and 13/249 (5.2%) patients receiving tamoxifen.

Results from the ATAC trial bone substudy at 12 and 24 months demonstrated that patients receiving anastrozole tablets 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.

Results from the ATAC trial bone substudy at 12 and 24 months demonstrated that patients receiving anastrozole tablets 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.

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

Post-marketing trial also evaluated any potential effects of anastrozole tablets on lipid profile. In the primary analysis and population for lipids (anastrozole tablets 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 tablets + risnedronate), 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 tablets alone had a neutral effect on lipid profile. Combination treatment with anastrozole tablets and risnedronate 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 tablets 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 tablets had an increase in joint disorders (including arthritis, arthrosis and arthralgia) compared with patients receiving tamoxifen. Patients receiving anastrozole tablets 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%)].

Vaginal bleeding occurred more frequently in the tamoxifen-treated patients versus the anastrozole tablets-treated patients 317 (10%) versus 167 (5%), respectively. Patients receiving anastrozole tablets 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 overall number of deaths (during or off-treatment) was similar between the treatment groups. There were more deaths related to breast cancer in the tamoxifen than in the anastrozole treatment group.

First-Line Therapy: Adverse reactions occurring with an incidence of at least 5% in either treatment group of trials 0030 and 0027 during or within 2 weeks of the end of treatment are shown in Table 3.

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\*Sections or subsections omitted from the full prescribing information are not listed

reported in greater than 5% of the patients in any of the treatment groups in these two controlled clinical trials, regardless of causality, are presented below:

Table 5: Number (N) and Percentage of Patients with Adverse Reactions in Trials 0004 and 0005. Columns: Adverse Reaction, Anastrozole 1mg, Anastrozole 10mg, Megestrol Acetate 160mg.

\*Patient may have had more than one adverse reaction. Other less frequent (2% to 5%) adverse reactions reported in patients receiving anastrozole tablets 1 mg in either Trial 0004 or Trial 0005 are listed below. These adverse experiences are listed by body system and are in order of decreasing frequency within each body system regardless of assessed causality.

Body as a Whole: Flu syndrome; fever; neck pain; malaise; accidental injury; infection. Cardiovascular: Hypertension; thrombophlebitis. Hepatic: Gamma GT increased; SGOT increased; SGPT increased. Hematologic: Anemia; leukopenia.

Musculoskeletal: Myalgia; arthralgia; pathological fracture. Nervous: Somnolence; confusion; insomnia; anxiety; nervousness. Respiratory: Sinusitis; bronchitis; rhinitis. Skin and Appendages: Hair thinning (alopecia); pruritus. Urogenital: Urinary tract infection; breast pain.

The incidences of the following adverse reaction groups potentially causally related to one or both of the therapies because of their pharmacology, were statistically analyzed: weight gain, edema, thromboembolic disease, gastrointestinal disturbance, hot flashes, and vaginal dryness. These six groups, and the adverse reactions captured in the groups, were prospectively defined. The results are shown in the table below.

Table 6: Number (n) and Percentage of Patients with Pre-specified Adverse Reactions in Trials 0004 and 0005. Columns: Adverse Reaction Group, Anastrozole 1mg, Anastrozole 10mg, Megestrol Acetate 160mg.

6.2 Post-Marketing Experience: Hepatobiliary events including increases in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase have been reported (>1% and <10% and gamma-GT, bilirubin and hepatitis have been reported (<0.1% and <1% in patients receiving anastrozole tablets).

Anastrozole tablets may also be associated with rash including cases of mucocutaneous disorders such as erythema multiforme and Stevens-Johnson syndrome. Cases of allergic reactions including angioedema, urticaria and anaphylaxis have been reported in patients receiving anastrozole tablets.

Trigger finger has been reported (>0.1% and <1%) in patients receiving anastrozole tablets. DRUG INTERACTIONS: 7.1 Tamoxifen

Co-administration of anastrozole and tamoxifen in breast cancer patients reduced anastrozole plasma concentration by 27%. However, the coadministration 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 tablets and tamoxifen did not demonstrate any efficacy benefit when compared with tamoxifen in all patients as well as in the hormone receptor-positive subpopulation. The 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-containing therapies should not be used with anastrozole tablets 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<sub>max</sub> 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 tablets 1 mg will affect other drugs as the result of inhibition of cytochrome P450 [see CLINICAL PHARMACOLOGY (12.3)].

8 USE IN SPECIFIC POPULATIONS: 8.1 Pregnancy: Pregnancy Category X [See CONTRAINDICATIONS (4.1)]. Anastrozole tablets may cause fetal harm when administered to a pregnant woman and offers no clinical benefit to premenopausal women with breast cancer. Anastrozole tablets is contraindicated in women who are or may become pregnant. In animal studies, anastrozole caused embryonic and fetal loss, and signs of delayed fetal development at doses equal to or greater than 1 (rats) and 1/3 (rabbits) the recommended human dose on a mg/m<sup>2</sup> 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<sub>0-24</sub>, 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<sup>2</sup> basis [see Animal Toxicology and/or Pharmacology (13.2)].

8.2 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 immunogenicity 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: The efficacy of anastrozole tablets 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. Labeling describing clinical trials and pharmacokinetic studies of anastrozole in pubertal boys of adolescent age with gynecomastia and in girls with McCune-Albright Syndrome and progressive precocious puberty is approved for AstraZeneca Pharmaceuticals LP's "Arimidex". However, due to AstraZeneca Pharmaceuticals LP's marketing exclusivity rights, a description of those trials and studies is not approved for this anastrozole product.

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 tablets compared to tamoxifen in patients who were 65 years or older (N=1413 for anastrozole tablets 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 tablets and N=1708 for tamoxifen), the hazard ratio for disease-free survival was 0.79 [95% CI: 0.67, 0.94].

The pharmacokinetics of anastrozole are 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. Dose 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 tablets have not been studied in patients with severe hepatic impairment [see DOSAGE AND ADMINISTRATION (2.2) and CLINICAL PHARMACOLOGY (12.3)].

10 OVERDOSAGE: Clinical studies have been conducted with anastrozole tablets, 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 tablets that results in life-threatening symptoms has not been established. There is no specific antidote to overdose 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 tablets is not highly protein bound. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

11 DESCRIPTION: Anastrozole tablets for oral administration contain 1 mg of anastrozole, a non-steroidal aromatase inhibitor. It is chemically described as 1,3-Benzoxindolecarboxylic acid, a, a', a''-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl). Its molecular formula is C<sub>17</sub>H<sub>14</sub>N<sub>4</sub> and its structural formula is:



Anastrozole, USP 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 dependent of pH in the physiological range. Anastrozole is freely soluble in methanol, acetone, ethanol, and tetrahydrofuran, and only-slightly in acetonitrile.

Each tablet contains as inactive ingredients: lactose, magnesium stearate, hydroxypropylmethylcellulose, polyethylene glycol, polyvidone, sodium starch glycolate, and titanium dioxide.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND 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.

2 DOSAGE AND 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 tablet 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 tablets were 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 tablet has not been studied in patients with severe hepatic impairment [see USE IN SPECIFIC POPULATIONS (8.7)].

3 DOSAGE FORMS AND STRENGTHS: The tablets are white, biconvex, round coated containing 1 mg of anastrozole. The tablets are debossed on one side with "A7" on one side and plain on the other side.

4 CONTRAINDICATIONS

4.1 Pregnancy and Premenopausal Women: Anastrozole tablets may cause fetal harm when administered to a pregnant woman and offers no clinical benefit to premenopausal women with breast cancer. Anastrozole tablets are contraindicated in women who are or may become pregnant. There are no adequate and well-controlled studies in pregnant women using anastrozole tablets. If anastrozole tablets are 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 tablets are 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)].

5 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 tablets in the ATAC trial (17% of patients on anastrozole tablets and 10% of patients on tamoxifen). Consider risk and benefits of anastrozole tablets 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 tablets had a mean decrease in both lumbar spine and total hip bone mineral density (BMD) compared to baseline. Patients receiving tamoxifen had

