ANASTROZOLE (Systemic)

Introduction
Commonly used brand name(s):Arimidex.

Indications

Accepted

Carcinoma, breast (treatment)¾Anastrozole is indicated for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed despite previous tamoxifen therapy 1, 3.

Note: Patients with E-R negative disease and patients who have had no response to previous tamoxifen therapy rarely respond to anastrozole 1.

Mechanism of action/Effect:

Anastrozole is a nonsteroidal aromatase inhibitor that interferes with estradiol production in peripheral tissues. Adrenally generated androstenedione, the chief source of circulating estrogen in postmenopausal women, is converted by aromatase to estrone, which is further converted to estradiol. Growth of many breast cancer tumors containing estrogen receptors and aromatase can be promoted by estrogen 1.

Onset of action:

A 70% reduction of serum estradiol usually occurs within 24 hours, with an 80% reduction in serum estradiol occurring after 14 days 1.

Time to peak concentration:

Steady state concentrations are achieved after approximately 7 days 1.

Duration of action:

Estrogen antagonism may persist for up to 6 days following the discontinuation of anastrozole 1.

Elimination:

Primary route¾Biliary 1 : Approximately 85% 1.

Secondary route¾Renal: Approximately 11% (about 10% unchanged and 60% as metabolites) 1.
1

Precautions to Consider

Carcinogenicity

Studies with anastrozole have not been done 1.

Mutagenicity

Anastrozole demonstrated no mutagenic effects in the Ames test, Escherichia coli bacterial test, Chinese hamster ovary-K1 mutation assay. It was not clastogenic in a in vitro chromosomal aberrationhuman lymphocyte assayor in ain vivo micronucleus test in rats 1, 2.

Pregnancy/Reproduction

Fertility¾Adequate and well-controlled studies in humans have not been done 1.

Long-term studies in rats, at dosesequal or greater than 1mg/kg/day (this dose produced plasma levels that were 9 to 19 times higher than the respective values found in healthy post-menopausal humans at the recommended dose.) 2 , have shown that anastrozole produces ovarian hypertrophy and follicular cysts. Studies in dogs have shown that anastrozole causes hyperplastic uteri at dosesequal to or greater than 1 mg/kg/day (this dose produced plasma levels that were 22 and 16 times higher than the respective values found in healthy post-menopausal humans at the recommended dose.) It is unknown if these effects on the reproductive organs of animals are associated with impairment of fertility in humans. 2, 1.

Pregnancy¾Adequate and well-controlled studies in humans have not been done 1.

Studies in rats and rabbits, at 75% and 150% of the recommended human dose, respectively, have shown that anastrozole crosses the placenta 1 .Rats and rabbits given doses of anastrazole during organogenesis that were equal to or greater than 0.1 and 0.02 mg/kg/day (about 75% and 33%, respectively, of the recommended human dose) showed increased pregnancy losses (increased pre- and/or post-implantation loss, increased resorption, and decreased numbers of live fetuses) and dose related effects in rats. Placental weights were significantly increased in rats at doses of 0.1 mg/kg/day or more. 2

Anastrozole is fetotoxic in rats, causing decreased fetal body weights, delayed fetal development and incomplete ossification, at doses that produce a plasma concentration 19 times and 9 times greater than the plasma concentration associated with the recommended human dose. 2 Anastrozole is not teratogenic in rats given doses up to 1.0 mg/kg per day. In rabbits at doses that produce plasma concentrations that are 19 and 3 times, respectively, greater than the plasma concentration associated with the recommended human dose. Studies in rabbits, at doses that produce a plasma concentration 16 times greater than the plasma concentration associated with the recommended human dose, have shown that anastrozole may cause pregnancy failure. Studies in rats, given 75% of the recommended human dose, have shown that anastrozole may cause an increase in placental weight 1, 2.

FDA Pregnancy Category D 1.

Breast-feeding

It is not known whether anastrozole is distributed into breast milk. However, breast-feeding is not recommended during anastrozole therapy because of the potential risks to the infant. 2

Pediatrics

No information is available on the relationship of age to the effects of anastrozole in pediatric patients. Safety and efficacy have not been established 1.

Geriatrics

Appropriate studies performed to date have have not demonstrated geriatrics-specific problems that would limit the usefulness of anastrozole in the elderly 1, 2.

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence more frequent

Chest pain 1; dyspnea 1 shortness of breath); edema, peripheral 1 swelling of feet or lower legs)
Incidence less frequent

Anemia 1unusual tiredness or weakness); hypertension 1dizziness, severe); continuing headache)¾usually asymptomatic ; leukopenia, with or without infection 1fever or chills); cough or hoarseness); lower back or side pain); painful or difficult urination); sore throat)¾usually asymptomatic; thromboembolism 1sudden shortness of breath); thrombophlebitis 1pain or tenderness in leg or foot); blue color in leg or foot); swelling of leg or foot); vaginal hemorrhage 1heavy vaginal bleeding)

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Asthenia 1 (weakness); anorexia (loss of appetite ; weight loss) 2; back pain 2; bone pain 1; cough 1; constipation 2; depression (mood or mental changes) 2; dizziness 1; dry mouth 1; flushing 1 (feeling of warmth; redness of face and neck); gastrointestinal disturbances, including abdominal pain, diarrhea, nausea, or vomiting 1; headache 1; hot flashes 1; increased appetite 2; pain 2; pelvic pain 1; pharyngitis (body aches or pain ; congestion ; cough ; dryness or soreness of throat ; fever; hoarseness ; runny nose ; tender, swollen glands in neck ; trouble in swallowing ; voice changes) 2; skin rash 1; sweating 1
Incidence less frequent

Anxiety and confusion 2; arthralgia 1 (joint pain); breast pain 1; bronchitis (cough producing mucus ; difficulty breathing; shortness of breath ; tightness in chest ; wheezing) 2; flu syndrome (chills ; cough; diarrhea ; fever ; general feeling of discomfort or illness; headache; joint pain ; loss of appetite ; muscle aches and pains ; nausea ; runny nose ; shivering ; sore throat ; sweating ; trouble sleeping; unusual tiredness or weakness ; vomiting) 2; insomnia (sleeplessness ; trouble sleeping; unable to sleep) 2; myalgia 1 (muscle pain); nervousness 2; paresthesia 1 (numbness or tingling sensation of hands and feet); pruritus 1 (itchy skin); sinusitis or rhinitis 1 (stuffy nose); somnolence (sleepiness or unusual drowsiness) 2; vaginal dryness 1; weight gain 1
Those not indicating need for medical attention

Incidence less frequent

Alopecia 1 (loss of hair)

Overdose

For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Note: Clinical trials have shown doses of 60 mg given in a single dose to male participants and doses up to 10 mg have been given to postmenopausal women with breast cancer and have been well tolerated. A single dose that results in life-threatening symptoms has not been established 2.

Treatment of overdose

Treatment is essentially symptomatic and supportive and may consist of the following:

Note: In the treatment of the overdose it is important to note that multiple agents may have been taken by the patient. 2

· Emptying the stomach via induction of emesis if patient is alert 1.

· Hemodialysis may be beneficial 1.

Supportive care¾ General supportive care such as monitoring vital signs and careful patient observation is suggested.
  Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Anastrozole (Systemic)¾Introductory Version .
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using taking this medication

>> Conditions affecting use, especially:

Pregnancy¾Use not recommended due to fetotoxic potential; telling physician immediately if pregnancy is suspected 1

Proper use of this medication

Importance of taking medication only as directed by physician; not taking more medication or more frequently than as ordered by physician

Importance of continuing medication even if nausea, vomiting, or diarrhea occurs

>> Proper dosing 1

>> Proper storage 1

Precautions while using this medication

Importance of close monitoring by physician 1

Side/adverse effects

Signs of potential side effects, especially chest pain; dyspnea; peripheral edema; anemia; hypertension; leukopenia, with or without infection; thromboembolism; thrombophlebitis; or vaginal hemorrhage 1