PACKAGE INSERT TEMPLATE FOR ANASTROZOLE TABLET

Brand or Product Name
[Product name] Tablet 1mg

Name and Strength of Active Substance(s)
Anastrozole 1mg

Product Description
[Visual description of the appearance of the product (eg colour, markings etc)]
eg White, circular flat beveled edge tablets marked '1' on one side

Pharmacodynamics
Many breast cancers have estrogen receptors and growth of these tumors can be stimulated by oestrogen. In postmenopausal women, the principal source of circulating oestrogen (primarily oestradiol) is conversion of adrenally generated androstenedione to estrone by aromatase in peripheral tissues with further conversion of oestrone to oestradiol. Many breast cancers also contain aromatase. Treatment of breast cancer has included efforts to decrease oestrogen levels.

Anastrozole is a potent and highly selective non-steroidal aromatase inhibitor. As with other aromatase inhibitors, anastrozole lowers oestrogen levels in postmenopausal women by inhibiting conversion of adrenally-generated androstenedione(adrenal androgens) to oestrone by aromatase in peripheral tissues. Oestrone is subsequently converted to oestradiol. Adrenally generated androstenedione is the chief source of circulating oestrogen in postmenopausal women
Reducing circulating oestradiol levels has been shown to produce a beneficial effect in women with breast cancer.

Anastrozole has no significant effect on cortisol or aldosterone (at baseline or in response to adrenocorticotropic hormone (ACTH)), and has not induced increases in thyroid-stimulating hormone (TSH) in patients. There has been no evidence of direct progestogenic, estrogenic, or androgenic activity with anastrozole.

Pharmacokinetics
There is no evidence of time or dose-dependency of anastrozole pharmacokinetic parameters.
Anastrozole pharmacokinetics is independent of age in postmenopausal women.

Absorption
The bioavailability of anastrozole was 80% after oral administration
Peak plasma concentrations occur within about 2 hours.
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 daily dosing of anastrozole tablets.
Plasma anastrozole steady-state concentrations are attained after 7 daily doses

Distribution
Anastrozole is 40% bound to plasma proteins

Metabolism
Hepatic metabolism via N-dealkylation, hydroxylation, and glucuronidation, accounts for approximately 85% of the elimination of anastrozole. The major circulating metabolite triazole, a glucuronide conjugate

of hydroxy-anastrozole, lacks pharmacologic activity. Hydroxy-anastrozole and anastrozole glucuronide, 2 other metabolites with unknown pharmacologic activity have been identified in plasma and urine. It has been hypothesized that differences in metabolism may contribute to the inter-individual variability in the drug's effects.

Elimination
The terminal plasma elimination half-life is about 40 to 50 hours.
85% of anastrozole is recovered in feces and urine. Renal elimination accounts for approximately 10% of the total clearance; with the approximate remainder of 75% of anastrozole recovered in feces.

Indication
Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.
Treatment of advanced breast cancer in post-menopausal women. Efficacy has not been demonstrated in oestrogen receptor negative patients unless they had a previous positive clinical response to tamoxifen.

Recommended Dosage
Adults including the elderly: One 1mg tablet to be taken orally once a day.

Children: Not recommended for use in children

Renal impairment: No dose change is recommended in patients with mild or moderate renal impairment.

Hepatic impairment: No dose change is recommended in patients with mild hepatic disease.

For early disease, the recommended duration of treatment should be 5 years.

Mode of Administration
Oral

Contraindications
Anastrozole is contra-indicated in:

- pre-menopausal women.
- pregnant or lactating women.
- patients with severe renal impairment (creatinine clearance less than 20ml/min).
- patients with moderate or severe hepatic disease.
- patients with known hypersensitivity to anastrozole or to any of the excipients as referenced in the list of excipients

Oestrogen-containing therapies should not be co-administered with anastrozole as they would negate its pharmacological action.

Concurrent tamoxifen therapy

Warnings and Precautions
Anastrozole is not recommended for use in children as safety and efficacy have not been established in this group of patients.

The menopause should be defined biochemically in any patient where there is doubt about hormonal status.

There are no data to support the safe use of Anastrozole in patients with moderate or severe hepatic impairment, or patients with severe impairment of renal function (creatinine clearance less than 20 ml/min).

Women with osteoporosis or at risk of osteoporosis, should have their bone mineral density (BMD) formally assessed at the start of therapy and at regular intervals thereafter by bone densitometry e.g. DEXA scanning at the commencement of treatment and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored.

There are no data available for the use of anastrozole with LHRH analogues. This combination should not be used outside clinical trials.

As Anastrozole lowers circulating oestrogen levels it may cause a reduction in bone mineral density with a possible consequent increased risk of fracture. The use of bisphosphonates may stop further bone mineral loss caused by anastrozole in postmenopausal women and could be considered.

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Effects on Ability to Drive and Use Machines
Anastrozole is unlikely to impair the ability of patients to drive and operate machinery. However, asthenia and somnolence have been reported with the use of and caution should be observed when driving or operating machinery while such symptoms persist.

Interactions with Other Medicaments
Co-administration of anastrozole with other drugs is unlikely to result in clinically significant drug interactions mediated by cytochrome P450 (eg antipyrine, cimetidine).

There were no clinically significant interactions with bisphosphonates.

Oestrogen-containing therapies should not be co-administered with anastrozole as they would negate its pharmacological action.

Concurrent use of anastrozole and tamoxifen may result in reduced anastrozole plasma levels
There is no evidence of clinically relevant interactions with other commonly prescribed drugs.

Statement on Usage During Pregnancy and Lactation
Anastrozole is contraindicated in pregnant and lactating women

Adverse Effects / Undesirable Effects
Cardiovascular: hypertension, peripheral edema, vasodilatation, chest pain, ischemic heart disease, myocardial infarction, thrombophlebitis

Psychiatric: anxiety, depression, disturbance in mood

Respiratory: dyspnea, increasing frequency of cough, pharyngitis, bronchitis, rhinitis, and sinusitis

Hematologic: anemia, deep venous thrombosis, leukopenia, thromboembolic disorder

Immunologic: immune hypersensitivity reaction, lymphedema

Neurologic: cerebral ischemia

Musculoskeletal, connective tissue and bone: reductions in bone mineral density, joint pain/stiffness, trigger finger, arthralgia, arthritis, backache, bone pain, osteoporosis, fracture of bone

Nervous system: asthenia, headache, somnolence, insomnia, carpal tunnel syndrome, dizziness, sensory disturbances (including paraesthesia, taste loss and taste perversion)

Gastrointestinal: nausea, diarrhea, vomiting

Skin and subcutaneous tissue: rash, hair thinning (alopecia), allergic reactions, urticaria, erythema multiforme, anaphylactic reaction, Stevens-Johnson Syndrome and angioedema

Hepatobiliary disorders: increases in alkaline phosphatase, alkaline amino-transferase, aspartate amino-transferase, gamma-GT and bilirubin, hepatitis

Reproductive system and breast: menopausal flushing, vaginal dryness, vaginal bleeding

Metabolism and nutrition: anorexia, hypercholesterolemia

Other: pain, cancer, tumor flare, cataracts, urinary-tract infections

Overdose and Treatment
There is no specific antidote to overdosage and treatment must be symptomatic.
In the management of an overdose, consideration should be given to the possibility 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.

Storage Conditions
[eg Store below….°C]

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]