PRESCRIBING INFORMATION

(For the Use of a Registered Medical Practitioner or a Hospital or Laboratory only)

ANAST 1

Anastrozole Tablets 1 mg

Name and strength of active ingredient

Anastrozole Ph. Eur. 1 mg

Product Description

White to off white, round, biconvex, film coated tablets with "AHI" debossing on one side and plain on other side.

Pharmacological properties

Pharmacodynamic properties

Anastrozole is a potent and highly selective nonsteroidal aromatase inhibitor. In postmenopausal women, estradiol is produced primarily from the conversion of androstenedione to estrone through the aromatase enzyme complex in peripheral tissues. Estrone is subsequently converted to estradiol. Reducing circulating estradiol levels has been shown to produce a beneficial effect in women with breast cancer. In postmenopausal women, Anastrozole at a daily dose of 1 mg produced estradiol suppression of greater than 80% using a highly sensitive assay.

Anastrozole does not possess any progestogenic, androgenic, or estrogenic activity.

Daily doses of Anastrozole up to 10 mg do not have any effect on cortisol or aldosterone secretion, measured before or after standard adrenocorticotrophic hormone (ACTH) challenge testing. Corticoid supplements are therefore not needed.

Pharmacokinetic properties

Absorption

Absorption of Anastrozole is rapid and maximum plasma concentrations typically occur within two hours of dosing (under fasted conditions). 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. Approximately 90 to 95% of plasma Anastrozole steady state concentrations are attained after 7 daily doses, and accumulation is 3 to 4 fold. There is no evidence of time or dose dependency of Anastrozole pharmacokinetic parameters. Anastrozole pharmacokinetics are independent of age in postmenopausal women.

Distribution

Anastrozole is only 40% bound to plasma proteins.

Elimination

Anastrozole is eliminated slowly with a plasma elimination half life of 40 to 50 hours. Anastrozole is extensively metabolized by postmenopausal women with less than 10% of the dose excreted in the urine unchanged within 72 hours of dosing. Metabolism of Anastrozole occurs by N-dealkylation, hydroxylation and glucuronidation. The metabolites are excreted primarily via the urine. Triazole, the major metabolite in plasma, does not inhibit aromatase.

Renal or hepatic impairment

The apparent clearance (CL/F) of Anastrozole, following oral administration, was approximately 30% lower in volunteers with stable hepatic cirrhosis than in matched controls (Study 1033IL/0014). However, plasma Anastrozole concentrations in the volunteers with hepatic cirrhosis were within the range of concentrations seen in normal subjects in other trials. Plasma Anastrozole concentrations observed during long term efficacy trials in patients with hepatic impairment were within the range of plasma Anastrozole concentrations seen in patients without hepatic impairment.

The apparent clearance (CL/F) of Anastrozole, following oral administration, was not altered in volunteers with severe renal impairment (GFR <30ml/min) in Study 1033IL/0018, consistent with the fact that Anastrozole is eliminated primarily by metabolism. Plasma Anastrozole concentrations observed during long term efficacy trials in patients with renal impairment were within the range of plasma Anastrozole concentrations seen in patients without renal impairment. In patients with severe renal impairment, administration of Anastrozole should be performed with caution.

Paediatric population

In boys with pubertal gynaecomastia (10-17 years), Anastrozole was rapidly absorbed, was widely distributed, and was eliminated slowly with a half life of approximately 2 days. Clearance of Anastrozole was lower in girls (3-10 years) than in the older boys and exposure higher. Anastrozole in girls was widely distributed and slowly eliminated.

Indication/Usage

Treatment of advanced breast cancer in postmenopausal women. Efficacy has not been demonstrated in oestrogen receptor negative patients unless they had a previous positive clinical response to tamoxifen.

Adjuvant treatment of postmenopausal women with hormone receptor positive early invasive breast cancer.

Adjuvant treatment of early breast cancer in hormone receptor positive postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen.

Recommended Dose

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

Children

Anastrozole Tablets is not recommended for use in children due to insufficient data on safety and efficacy (see sections 4.4 and 5.1)

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.

Route of Administration

Oral use

Contraindication

Anastrozole is contraindicated in:

- Patients with known hypersensitivity to Anastrozole or to any of the excipients
- Premenopausal women.
- Pregnant or lactating women.
- Patients with moderate or severe hepatic disease.
- Oestrogen containing therapies should not be co administered with Anastrozole as they would negate its pharmacological action.
- Concurrent tamoxifen therapy.

Special warnings and precautions for use

General

Anastrozole should not be used in premenopausal women. The menopause should be defined biochemically (luteinizing hormone [LH], follicle stimulating hormone [FSH], and/or estradiol levels) in any patient where there is doubt about menopausal status. There are no data to support the use of Anastrozole with LHRH analogues. Co-administration of tamoxifen or estrogencontaining therapies with Anastrozole should be avoided as this may diminish its pharmacological action.

Effect on bone mineral density

As Anastrozole lowers circulating estrogen levels it may cause a reduction in bone mineral density with a possible consequent increased risk of fracture.

Women with osteoporosis or at risk of osteoporosis should have their bone mineral density formally assessed at the commencement of treatment and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored. The use of specific treatments, e.g., bisphosphonates, may stop further bone mineral loss caused by Anastrozole in postmenopausal women and could be considered.

Hepatic impairment

Anastrozole has not been investigated in breast cancer patients with moderate or severe hepatic impairment. Exposure to Anastrozole can be increased in subjects with hepatic impairment, administration of Anastrozole in patients with moderate and severe hepatic impairment should be performed with caution. Treatment should be based on a benefit risk evaluation for the individual patient.

Renal impairment

Anastrozole has not been investigated in breast cancer patients with severe renal impairment. Exposure to Anastrozole is not increased in subjects with severe renal impairment (GRF<30ml/min), in patients with severe renal impairment, administration of Anastrozole should be performed with caution.

Paediatric population

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

Anastrozole should not be used in boys with growth hormone deficiency in addition to growth hormone treatment. In the pivotal clinical trial, efficacy was not demonstrated and safety was not established. Since Anastrozole reduces estradiol levels, Anastrozole must not be used in girls with growth hormone deficiency in addition to growth hormone treatment. Long term safety data in children and adolescents are not available.

Hypersensitivity to lactose

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

Interaction with other medicinal products and other forms of interaction

Anastrozole inhibits CYPs 1A2, 2C8/9 and 3A4 in vitro. Clinical studies with antipyrine and warfarin showed that Anastrozole at a 1 mg dose did not significantly inhibit the metabolism of antipyrine and R and S-warfarin indicating the co-administration of Anastrozole with other medicinal products is unlikely to result in clinically significant medicinal product interactions mediated by CYP enzymes.

The enzymes mediating metabolism of Anastrozole have not been identified. Cimetidine, a weak, unspecific inhibitor of CYP enzymes, did not affect the plasma concentrations of Anastrozole. The effect of potent CYP inhibitors is unknown.

A review of the clinical trial safety database did not reveal evidence of clinically significant interaction in patients treated with Anastrozole who also received other commonly prescribed medicinal products. There were no clinically significant interactions with bisphosphonates. Co-administration of tamoxifen or estrogencontaining therapies with Anastrozole should be avoided as this may diminish its pharmacological action.

Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Anastrozole in pregnant women. Studies in animals have shown reproductive toxicity. Anastrozole is contraindicated during pregnancy.

Breast feeding

There are no data on the use of Anastrozole during lactation. Anastrozole is contraindicated during breast feeding.

Fertility

The effects of Anastrozole on fertility in humans have not been studied. Studies in animals have shown reproductive toxicity.

Effects on ability to drive and use machines

Anastrozole has no or negligible influence on the ability to drive and use machines. However, asthenia and somnolence have been reported with the use of Anastrozole and caution should be observed when driving or operating machinery while such symptoms persist.

Side effects/Adverse Reactions

The following table presents adverse reactions from clinical trials, post marketing studies or spontaneous reports.

Unless specified, the frequency categories were calculated from the number of adverse events reported in a large phase III study conducted in 9,366 postmenopausal women with operable breast cancer given adjuvant treatment for five years (the Anastrozole, Tamoxifen, Alone or in Combination [ATAC] study).

Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency groupings are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to <1/1,000), and very rare (<1/10,000). The most frequently reported adverse reactions were headache, hot flushes, nausea, rash, arthralgia, joint stiffness, arthritis, and asthenia.

Table 1 Adverse reaction by System Organ Class and frequency

Metabolism and nutrition disorders	
Common:	Anorexia, Hypercholesterolaemia
Uncommon:	Hypercalcaemia (with or without an increase in parathyroid hormone)
Nervous system disorders	
Very common:	Headache
Common:	Somnolence, Carpal Tunnel Syndrome*, Sensory disturbances (including paraesthesia, taste loss and taste perversion)
Vascular disorders	
Very Common:	Hot flushes
Gastrointestinal disorders	
Very common:	Nausea
Common:	Diarrhoea, Vomiting
Hepatobiliary disorders	
Common:	Increases in alkaline phosphatase, alanine amino transferase and aspartate aminotransferase
Uncommon:	Increases in gamma-GT and bilirubin, Hepatitis
Skin and subcutaneous tissue disorders	
Very common:	Rash
Common:	Hair thinning (alopecia), allergic reactions
Uncommon:	Urticaria
Rare:	Erythema multiforme, Anaphylactoid reaction, Cutaneous vasculitis (including some reports of Henoch-Schonlein purpura)**
Very rare:	Stevens Johnson syndrome Angioedema
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia/joint stiffness, Arthritis, Osteoporosis
Common:	Bone pain, Myalgia
Uncommon:	Trigger finger
Reproductive system and breast disorders	
Common:	Vaginal dryness, Vaginal bleeding***
General disorders and administration site conditions	
Very common:	Asthenia

* Events of Carpal Tunnel Syndrome have been reported in patients receiving Anastrozole treatment in clinical trials in greater numbers than those receiving treatment with tamoxifen. However, the majority of these events occurred in patients with identifiable risk factors for the development of the condition.

** Since cutaneous vasculitis and Henoch-Schönlein purpura was not observed in ATAC, the frequency category for these events can be considered as 'Rare' (≥1/10,000 to 1/1,000) based on the worst value of the point estimate.

*** Vaginal bleeding has been reported commonly, mainly in patients with advanced breast cancer during the first few weeks after changing from existing hormonal therapy to treatment with Anastrozole. If bleeding persists, further evaluation should be considered.

Overdose

There is limited clinical experience of accidental over dosage. In animal studies, Anastrozole demonstrated low acute toxicity. Clinical trials have been conducted with various dosages of 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 well tolerated. A single dose of Anastrozole that results in life threatening symptoms has not been established. There is no specific antidote to over dosage 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.

Ingredients

Active ingredient

Anastrozole

Inactive ingredient

Core tablet:
Lactose Monohydrate
Povidone K30
Sodium Starch Glycolate (Type A)
Magnesium Stearate
Coating:
Hypromellose E5
Macrogol 300 (PEG)
Titanium Dioxide

Storage Conditions

Do not store above 25°C.

Dosage forms and packaging available

ANAST 1 is available in PVC/PVDC –Alu Blister pack of 10 tablets, each carton contains 3 Blisters.

Manufactured by:

INTAS

INTAS PHARMACEUTICALS LTD.
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