

DATA SHEET

DP-ANASTROZOLE

Anastrozole 1 mg Film-coated Tablet

Name of the Medicine

DP-ANASTROZOLE

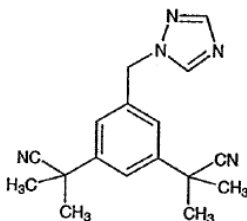
Anastrozole 1 mg Film-coated Tablet.

Description

Anastrozole is a benzyltriazole derivative. The chemical name is $\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-benzenediacetonitrile.

Anastrozole is a white to off-white powder. The chemical formula of Anastrozole is $C_{17}H_{19}N_5$ and the molecular weight is 293.4.

The molecular structure is:



DP-ANASTROZOLE 1 mg also contains as excipients lactose monohydrate, povidone, sodium starch glycolate type A, magnesium stearate, hypromellose and Opadry White Y-1-7000 (contains hypromellose, titanium dioxide and macrogol 400).

Pharmacology

Mechanism of Action

DP-ANASTROZOLE 1 mg is a potent and highly selective nonsteroidal aromatase inhibitor.

DP-ANASTROZOLE 1 mg selectively inhibits the conversion of androgens to estrogens, without affecting synthesis of adrenal corticosteroid, aldosterone or thyroid hormone.

In post-menopausal women, ovarian secretion of estrogen declines, and conversion of adrenal androgens into estrone and estradiol in peripheral tissues, catalysed by the aromatase enzyme (estrogen synthase) is the principal source of estrogens. Anastrozole selectively inhibits the conversion of androgens to estrogens by inhibiting the aromatase enzyme complex through competitive binding to the haeme of the cytochrome P450 (CYP450) unit of the enzyme. Suppression of estrogen biosynthesis in all tissues reduces serum concentrations of circulating estrogens, including estrone, estradiol, and estrone

sulphate with a subsequent beneficial effect in breast cancer. The suppression of estradiol production after a 1 mg dose has been measured at greater than 80%. Because of this mode of action, aromatase inhibitors are suitable only for post-menopausal women with ER-positive disease.

Anastrozole has been shown to be an effective treatment of early and advanced breast cancer in post-menopausal women. In a trial of 9366 post-menopausal women with operable breast cancer, it was shown to be statistically superior to tamoxifen in recurrence-free survival especially in patients with receptor positive status. Administration of anastrozole also significantly reduced the incidence of contralateral breast cancer and time to distant recurrence was also numerically superior. There was no efficacy benefit seen when anastrozole was administered in combination with tamoxifen when compared to administration of tamoxifen alone.

In a further trial of 2579 post-menopausal women with hormone receptor positive early breast cancer treated with adjuvant tamoxifen, anastrozole provided a superior disease-free survival in patients switched to anastrozole from tamoxifen in comparison to patients continuing on tamoxifen. Time to recurrence whether local or distant was also statistically better for those switched to anastrozole. The incidence of contralateral breast cancer had a numerical advantage for anastrozole although the incidence was very low in each treatment arm.

Other trials have supported these results and the safety profile was consistent with the known safety profile in post-menopausal women with hormone-receptor positive early breast cancer.

Pharmacokinetics

Absorption

Anastrozole is rapidly absorbed into the systemic circulation and the bioavailability is high following oral administration. Anastrozole is not subject to presystemic metabolism. Maximum plasma concentrations of anastrozole are reached within 2 hours after oral ingestion. Administration of daily doses of anastrozole achieved 90-95 % of plasma steady-state concentrations after 7 days. Maximal suppression of estrogens occurs after 3-4 days, and anastrozole reduces plasma estradiol levels in breast cancer patients by >80%.

Food decreases the rate of absorption, although this is not considered clinically significant, as the extent of absorption is unchanged.

There is no time or dose-dependency of anastrozole pharmacokinetic parameters.

Distribution

Within the therapeutic plasma concentration range, anastrozole is approximately 40 % bound to plasma proteins. It is not known whether anastrozole crosses the placenta

in humans; however, the drug has been shown to cross the placenta in rats and rabbits. It is not known whether anastrozole is distributed into milk in humans.

Metabolism

Anastrozole is extensively metabolised in the liver, and hepatic metabolism accounts for about 85 % of the elimination. Metabolism of anastrozole occurs via N-dealkylation, hydroxylation and glucuronidation. Three main metabolites have been identified in human plasma and the main aromatase-inhibiting activity of anastrozole results from the parent drug and these metabolites.

Elimination

The plasma elimination half-life of anastrozole following oral administration in post-menopausal women is between 40-50 hours. Renal excretion of anastrozole represents a minor route of elimination with <10% excreted as unchanged anastrozole within 72 hours of dosing. As mentioned previously, hepatic metabolism accounts for about 85 % of the elimination of anastrozole.

Special Populations

Among healthy post-menopausal women and female patients with breast cancer, no age-related differences in pharmacokinetics for anastrozole have been observed in women older than 80 years of age compared with women younger than 50 years of age.

The apparent oral clearance of anastrozole was reduced by approximately 30 % in individuals with stable hepatic cirrhosis related to alcohol abuse compared with controls with normal hepatic function. However, plasma anastrozole concentrations observed in individuals with hepatic cirrhosis were within the range of concentrations observed in normal individuals across all clinical trials.

Although the renal clearance of anastrozole decreases proportionally with creatinine clearance and is reduced by about 50 % in individuals with severe renal impairment (creatinine clearance < 30 mL/min per 1.73 m²) compared with controls, no reduction in total body clearance of anastrozole is observed in patients with severe renal impairment. This is because renal elimination is not a significant pathway of elimination, so dosing adjustment in patients with renal dysfunction is usually not necessary.

Clinical Trials

Acute toxicity

The median lethal dose of anastrozole in rodents after oral administration was >100 mg/kg and after intraperitoneal administration was > 50 mg/kg. The median lethal dose in a dog study was > 45 mg/kg.

Chronic Toxicity

The toxicity of multiple doses of anastrozole was studied using rats and dogs. The effects observed at the low dose (1 mg/kg/day) and mid doses (dog 3 mg/kg/day; rat 5 mg/kg/day) were related to the pharmacological and/or enzyme inducing properties of

anastrozole. These doses did not produce toxic or degenerative changes in either the rat or the dog.

Reproductive toxicology

No teratogenic effects were seen after oral administration of anastrozole to pregnant rats and rabbits at doses up to 1 mg/kg/day and 0.2 mg/kg/day respectively. Placental enlargement in rats and pregnancy failure in rabbits were seen, however, these effects are related to the pharmacology of anastrozole.

A high incidence of infertility at 1 mg/kg/day and increased pre-implantation loss at 0.02 mg/kg/day were seen after oral administration of anastrozole to female rats. These effects are related to the pharmacology of anastrozole. The effects were completely reversed 5 weeks after discontinuing administration of anastrozole.

Anastrozole given to rats at a dose of 0.02 mg/kg/day and above (from day 17 of pregnancy to day 22 post-partum) compromised the survival of their litters due to pharmacological effects on parturition. No adverse effects on behaviour or reproductive performance of the first generation offspring attributable to maternal treatment with anastrozole were found.

Mutagenicity

Anastrozole is not a mutagen or a clastogen.

Carcinogenicity

A 2-year oncogenicity study in rats showed an increase in the incidence of hepatic neoplasms and uterine stromal polyps in females at the high dose (25 mg/kg/day) only. Similarly an increase in incidence of thyroid adenomas occurred in males at the high dose (25 mg/kg/day) only. This dose represents a 100-fold greater exposure than occurs at human therapeutic doses. The effects are considered not clinically relevant to anastrozole treatment in humans.

Induction of benign ovarian tumours and a disturbance in the incidence of lymphoreticular neoplasms (fewer histiocytic sarcomas in females and more deaths as a result of lymphoma) was seen in a 2-year oncogenicity study in mice. The changes are considered to be mouse-specific effects of aromatase inhibition and are not clinically relevant to the anastrozole treatment in humans.

Indications

DP-ANASTROZOLE 1 mg is indicated for:

- Treatment of advanced breast cancer in post-menopausal women.

Contraindications

Anastrozole is contraindicated in:

- Patients with known hypersensitivity to anastrozole or any of the excipients included in the tablets.
- Pregnant or lactating women

Precautions

General

DP-ANASTROZOLE 1 mg is not recommended in premenopausal women as safety and efficacy has not been established for this group of patients.

DP-ANASTROZOLE 1 mg lowers circulating estrogen levels and may cause reduction of bone mineral density. This can increase the risk of osteoporosis for patients receiving anastrozole especially with long-term use, and bone mineral density should be monitored by bone densitometry.

Use in Pregnancy

Anastrozole has a Category C listing in the 4th edition of “Prescribing Drugs in Pregnancy” issued by the TGA. As anastrozole disrupts estrogen dependant metabolism, this may result in abortion. As it is unknown if anastrozole crosses the placenta DP-ANASTROZOLE 1 mg is contraindicated in pregnant women.

Use in Lactation

It is not known whether anastrozole is distributed into human milk. DP-ANASTROZOLE 1 mg is therefore contraindicated in lactating women.

Use in Children

DP-ANASTROZOLE 1 mg is not recommended for use in children as safety and efficacy has not been established for this group of patients.

Other Precautions

There is 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 < 20 mL/min). The risk/benefit ratio should be carefully considered prior to administration of DP-ANASTROZOLE™ 1 mg tablets.

Effects on Ability to Drive or Operate Machinery

DP-ANASTROZOLE 1 mg is unlikely to impair the ability of patients to drive or operate machinery. However, asthenia and somnolence have been reported and caution should be taken while such symptoms persist.

Interactions with other Medicines

Concomitant use of tamoxifen and/or other treatment regimens containing estrogens should not be used with anastrozole, as it’s pharmacological actions may be reduced.

High concentrations of anastrozole have been shown *in vitro* to inhibit metabolic reactions catalysed by cytochrome P450 (CYP450) isozymes, specifically 1A2, 2C8/9 and 3A4. It is, however, considered unlikely that DP-ANASTROZOLE 1 mg tablets will result in any clinically important interactions when administered at the recommended dosage.

Specific studies have shown no clinically significant interactions between anastrozole and warfarin, cimetidine, antipyrine or biphosphonates.

Adverse effects

Clinical experience shows that anastrozole is generally well tolerated. Adverse effects reported with anastrozole are similar to those reported with other aromatase inhibitors such as tamoxifen. Most of the adverse events are mild or moderate in nature and do not require modification or discontinuation of therapy.

Very Common ($\geq 10\%$)

- Hot flushes

Common ($\geq 1\%$ and $< 10\%$)

- Gastrointestinal upsets including nausea and diarrhoea
- Headache
- Rash
- Loss of hair
- Vaginal dryness
- Asthenia, joint pain or stiffness
- Carpal Tunnel Syndrome*
- Increases in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase

Uncommon ($\geq 0.1\%$ and $< 1\%$)

- Anorexia
- Vomiting
- Somnolence
- Hypercholesterolemia
- Vaginal bleeding**
- Increases in gamma-GT and bilirubin
- Hepatitis

Very Rare ($< 0.1\%$)

- Allergic reactions (including angioedema, urticaria and anaphylaxis)
- Stevens-Johnson syndrome
- Erythema multiforme

* Clinical trials with anastrozole have reported a higher incidence of Carpal Tunnel Syndrome than trials with tamoxifen. Many of these patients had risk factors predisposing them to this syndrome.

** Vaginal bleeding is an uncommon side effect that has been reported. This occurs 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.

A large phase III study conducted for 5 years, in postmenopausal women with operable breast cancer, documented an increased incidence of ischaemic cardiovascular events in patients taking anastrozole compared to those taking tamoxifen. This difference was not statistically significant and was mainly due to more reports of angina pectoris associated with a sub-group of patients with pre-existing ischaemic heart disease.

Dosage and Administration

Dosage recommendations for DP-ANASTROZOLE 1 mg film-coated tablets	
Adults including the elderly:	One 1 mg tablet to be taken orally once a day.
Children:	Not recommended for use in children.
Renal impairment:	No dose adjustment is recommended.
Hepatic impairment:	No dose adjustment is recommended.

DP-ANASTROZOLE 1 mg tablets are presented in a calendar pack of 30 tablets. Within each pack there are two blister trays, each containing 15 tablets. The patient should start taking the tablets from one tray on the relevant day of the week and complete that tray by taking one tablet daily according to the days shown on the tray. Once all tablets have been taken from the tablet pockets marked with the day of the week, they should complete the tray by taking the tablet from the pocket marked "Take Last". On the next day, the patient should start the second blister tray by taking the first tablet from the relevant day of the week and continuing to completion as for the first tray.

Overdosage

There is limited information available on the overdosage and acute toxicity of anastrozole. A range of doses have been given during clinical studies 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.

In the management of overdose, there is no specific treatment. Concomitant medications should be ruled out before treatment. Vomiting may be induced if the patient is alert, and dialysis may be helpful as anastrozole is not highly protein bound. General supportive care is indicated including close observation of the patient and vital signs should be monitored.

Presentation and Storage conditions

DP-ANASTROZOLE 1 mg film-coated tablets are white to off-white, round, film-coated, biconvex tablets engraved with “A 1” on one side and plain on the other. The tablets contain lactose (see Description) and are gluten-free.

Storage

DP-ANASTROZOLE 1 mg tablets should be stored below 30 °C and should be kept in a place where they will remain dry and away from light. The shelf-life is 36 months.

Pack quantities

DP-ANASTROZOLE 1 mg Tablets are available in calendar blister packs of 30 tablets and bottle packs of 30 or 90 tablets.

Medicine Classification

Prescription Medicine.

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