PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

EVERDEX® 1 mg, Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg anastrozole.

Contains sugar: lactose monohydrate 93 mg

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablets

Round, white, biconvex film-coated, intagliated tablets, impressed with a logo consisting of the letter 'A' with an arrow head attached to the foot of the extended right leg of the 'A', on one side and a tablet strength marking ('Adx 1') on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of early breast cancer in postmenopausal women.

Treatment of advanced breast cancer in postmenopausal women.

Efficacy has not been demonstrated in oestrogen receptor negative patients unless they have had a previous positive clinical response to tamoxifen.

4.2 Posology and method of administration

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 change is recommended in patients with mild or moderate renal impairment.

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

4.3 Contraindications

EVERDEX is contraindicated in:

- patients with hypersensitivity to the active substance or to any of the excipients of EVERDEX (see section 6.1)
- pre-menopausal women
- pregnancy and lactation (see section 4.6)
- patients with severe renal impairment (creatinine clearance less than 20 ml/min)
- patients with moderate or severe hepatic disease

4.4 Special warnings and precautions for use

As EVERDEX lowers circulating oestrogen levels it may cause a reduction in bone mineral density with a consequent increased risk of fracture. This increased risk should be managed according to treatment guidelines for managing bone health in postmenopausal women.

EVERDEX is not recommended for use in pre-menopausal women as safety and efficacy have not been established in this group of patients.

EVERDEX 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 EVERDEX in patients with moderate or severe hepatic impairment or patients with severe impairment of renal function (creatinine clearance < 20 ml/min) (see section 4.3).

Lactose:

EVERDEX contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take EVERDEX.

4.5 Interaction with other medicines and other forms of interaction

Antipyrine and cimetidine clinical interaction studies indicate that the co-administration of EVERDEX with other medicines is unlikely to result in clinically significant interactions mediated by cytochrome P450.

A review of the clinical trial safety database did not reveal evidence of clinically significant interaction in patients treated with EVERDEX who also received other commonly prescribed medicines. There were no clinically significant interactions with bisphosphonates**.**

There is no clinical information to date on the use of EVERDEX in combination with other anti-cancer agents. Tamoxifen and/or oestrogen-containing therapies should not be co- administered with EVERDEX, as they would diminish its pharmacological action.

4.6 Fertility, pregnancy and lactation

EVERDEX is contraindicated in pregnancy and lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

Asthenia and somnolence have been reported with the use of EVERDEX and caution should be observed when driving or operating machinery while such symptoms persist.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequently reported adverse reactions were headache, hot flushes, nausea, rash, arthralgia, joint stiffness, arthritis, and asthenia

b. **Tabulated summary of adverse reactions**

The following side effects have been reported from clinical trials, post-marketing studies or spontaneous reports.

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); very rare (< 1/10 000).

System Organ Class	**Frequency**	**Adverse reactions**
Metabolism and nutrition disorders	Common	Anorexia; hypercholesterolaemia
	Uncommon	Hypercalcaemia (with or without an increase in parathyroid hormone)*
Psychiatric disorders	Very Common	Depression
Nervous system disorders	Very Common	Headache
	Common	Carpal tunnel syndrome; somnolence; sensory disturbances (including paraesthesia, taste loss and taste perversion)
Vascular disorders	Very Common	Hot flushes

Gastro-intestinal disorders	Very Common	Nausea
	Common	Diarrhoea; vomiting
Hepato-biliary disorders	Common	Increase in alkaline phosphatase*, alanine aminotransferase* and aspartate aminotransferase*
	Uncommon	Increase in gamma-GT and bilirubin*; hepatitis*
Skin and subcutaneous tissue disorders	Very Common	Rash*
	Common	Hair thinning (alopecia); allergic reactions*
	Uncommon	Urticaria*
	Rare	Erythema multiformae*; anaphylactoid reaction*, cutaneous vasculitis (including some reports of Henoch-Schönlein 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[1]
General disorders and administration site conditions	Very Common	Asthenia
[1] 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 EVERDEX. If bleeding persists, further evaluation should be considered. *Also reported in post-marketing studies or spontaneous reports		

Post-marketing experience:

No additional side effects are reported other than those already included in clinical trials, see * in Table above.

c. Description of selected adverse reactions

In a large phase III study conducted in 9 366 postmenopausal women with operable breast cancer treated for 5 years, ischaemic cardiovascular events were reported more frequently in patients treated with EVERDEX compared to those treated with tamoxifen, although the difference was not statistically significant. The observed difference was mainly due to more reports of angina pectoris and was associated with a sub-group of patients with pre-existing ischaemic heart disease.

Thromboembolism, fluid retention and dizziness have also been observed in clinical trials with EVERDEX.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is limited clinical experience of overdose of EVERDEX.

There are no reports where a patient has taken a dose exceeding 60 mg. No toxicity was observed and no clinically relevant adverse effects have been seen.

Acute toxicity was seen in animals at a dose greater than 45 mg/kg (equivalent to 2,7 g). Clinical trials have been conducted with various dosages of EVERDEX, 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 EVERDEX that results in life threatening symptoms has not been established. Refer to section 4.8 in the case of an overdose.

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 EVERDEX is not highly protein bound. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

5 PHARMACOLOGICAL PROPERTIES

A 21.12 Hormone inhibitors

5.1 Pharmacodynamic properties

Anastrozole is a selective non-steroidal aromatase inhibitor. It inhibits the conversion of androstenedione to estrone through the aromatase enzyme complex in peripheral tissues where estrone is subsequently converted to oestradiol. In postmenopausal women, anastrozole at a daily dose of 1 mg produced oestradiol suppression of greater than 80 %. Anastrozole does not possess any progestogenic, androgenic or oestrogenic activity. Anastrozole does not have any effect on cortisol or aldosterone secretion, measured before or after standard ACTH challenge testing.

5.2 Pharmacokinetic properties

Absorption of anastrozole is rapid and maximum plasma concentrations occur after 2 hours of dosing under fasted conditions. Anastrozole is eliminated slowly with a plasma elimination half-life of 40-50 hours. Food decreases the rate but not the extent of absorption. Approximately 90-95 % of plasma anastrozole steady-state concentrations are attained after 7 daily doses. There is no evidence of time or dose-dependency of anastrozole pharmacokinetic parameters.

Anastrozole pharmacokinetics are independent of age in postmenopausal women.

Pharmacokinetics have not been studied in children.

Anastrozole is only 40 % bound to plasma proteins.

Anastrozole is extensively metabolised 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, a major metabolite in plasma and urine, does not inhibit aromatase.

The apparent oral clearance of anastrozole in volunteers with mild stable hepatic cirrhosis or mild renal impairment was in the range observed in healthy volunteers.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose

Lactose monohydrate

Magnesium stearate

Macrogol 300

Povidone

Sodium starch glycollate

Titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

60 months

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

PVC/aluminium foil blister packs of 30 tablets in a carton.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

AstraZeneca Pharmaceuticals (Pty) Ltd

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17 Georgian Crescent West

Bryanston, Johannesburg, 2191

8 REGISTRATION NUMBER

42/21.12/1096

9 DATE OF FIRST AUTHORISATION

20 April 2012

10 DATE OF REVISION OF THE TEXT

22 January 2022

AstraZeneca Logo