PROFESSIONAL INFORMATION:

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

TEVA ANASTROZOLE 1 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each film-coated tablet contains 1 mg anastrozole.

TEVA ANASTROZOLE 1 mg contains sugar: (87,00 mg lactose monohydrate per film-coated tablet).

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Film-coated tablets.

White to off white, film-coated round shaped tablet. One side of the tablet debossed with the number '93'. The other side of the tablet debossed with the number 'A10'.

4. CLINICAL PARTICULARS:

4.1. Therapeutic indications:

TEVA ANASTROZOLE 1 mg is indicated for the 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.

Patients with renal impairment:

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

Patients with hepatic impairment:

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

4.3. Contraindications:

TEVA ANASTROZOLE 1 mg is contraindicated in:

- Pre-menopausal women.
- Pregnant or lactating women (See **section 4.6**).
- Patients with severe renal impairment (creatinine clearance less than 20 ml/min).
- Patients with moderate or severe hepatic disease.
- Patients with hypersensitivity to anastrozole or to any of the excipients as listed in **section 6.1**.

4.4 Special warnings and precautions for use:

General:

The menopause should be defined biochemically (luteinizing hormone [LH], follicle stimulating hormone [FSH], and/or oestradiol levels) in any patient where there is doubt about hormonal status. TEVA ANASTROZOLE 1 mg should not be used in pre-menopausal women. There are no data to support the use of TEVA ANASTROZOLE 1 mg with LHRH analogues.

Co-administration of tamoxifen or oestrogen-containing therapies with TEVA ANASTROZOLE 1 mg

should be avoided as this may diminish its pharmacological action (see **sections 4.5** and **5.1**).

Effect on bone mineral density:

TEVA ANASTROZOLE 1 mg can increase the risk of fractures, due to the fact that anastrozole lowers circulating oestrogen levels which may cause a reduction in bone mineral density.

Women with osteoporosis or women 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 TEVA ANASTROZOLE 1 mg in postmenopausal women and could be considered (see **section 4.8**).

Hepatic impairment:

TEVA ANASTROZOLE 1 mg 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 (see **section 5.2**); administration of TEVA ANASTROZOLE 1 mg in patients with moderate and severe hepatic impairment should be performed with caution (see **section 4.2**).

Renal impairment:

TEVA ANASTROZOLE 1 mg 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 < 30 ml/min, see **section 5.2**); in patients with severe renal impairment, administration of TEVA ANASTROZOLE 1 mg should be performed with caution (see **section 4.2**).

Paediatric population:

TEVA ANASTROZOLE 1 mg is not recommended for use in children and adolescents, as safety and efficacy have not been established in this group of patients (see **section 5.1**).

TEVA ANASTROZOLE 1 mg 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 (see **section 5.1**). Since anastrozole reduces oestradiol levels, TEVA ANASTROZOLE 1 mg 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.

TEVA ANASTROZOLE 1 mg contains lactose:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take TEVA ANASTROZOLE 1 mg.

Sodium content:

TEVA ANASTROZOLE 1 mg contains less than 1 mmol sodium (23 mg) per tablet, essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction:

Anastrozole inhibits CYPs 1A2, 2C8/9 and 3A4 *in vitro*. Clinical studies with antipyrine and warfarin showed that TEVA ANASTROZOLE 1 mg dose did not significantly inhibit the metabolism of antipyrine and R– and S-warfarin indicating the co-administration of TEVA ANASTROZOLE 1 mg 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 TEVA ANASTROZOLE 1 mg who also received other commonly prescribed medicinal products. There were no clinically significant interactions with bisphosphonates (see **section**

5.1).

Oestrogen-containing therapies should not be co-administered with TEVA ANASTROZOLE 1 mg; concomitant use may diminish the pharmacological action of anastrozole. Tamoxifen should not be co-administered with TEVA ANASTROZOLE 1 mg, as this results in a reduction of anastrozole plasma levels (see **sections 4.4** and **5.1**).

4.6 Fertility, pregnancy and lactation:

Pregnancy:

There are no data from the use of TEVA ANASTROZOLE 1 mg in pregnant women. Studies in animals have shown reproductive toxicity (see **section 5.3**). TEVA ANASTROZOLE 1 mg is contraindicated in pregnant women (see **section 4.3**).

Breastfeeding:

There is no data on the use of TEVA ANASTROZOLE 1 mg during lactation. TEVA ANASTROZOLE 1 mg is contraindicated during breastfeeding (see **section 4.3**).

Fertility:

The effects of TEVA ANASTROZOLE 1 mg on fertility in humans have not been studied.

4.7 Effects on the ability to drive and use machines:

TEVA ANASTROZOLE 1 mg is unlikely to impair the ability of patients to drive and operate machinery. However, asthenia and somnolence have been reported with the use of TEVA ANASTROZOLE 1 mg and caution should be observed when driving or operating machinery while such symptoms persist.

4.8 Undesirable effects:

Summary of the safety profile:

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

Tabulated list of adverse reactions:

System organ class	**Frequent**	**Less frequent**	**Frequency not known**
Blood and lymphatic system disorders		Anaemia, leukopenia, with or without infection, thromboembolism,thrombophlebitis.	
Metabolism and nutrition disorders	Anorexia,hypercholesterolaemia.	Hypercalcaemia (with or without an increase in parathyroid hormone), increased appetite, weight gain.	
Psychiatric disorders	Depression.		
Nervous system disorders	Dizziness, headache, somnolence, sensory disturbance (including paraesthesia, taste loss and taste perversion), carpal tunnel syndrome*.	Anxiety, confusion; insomnia, nervousness.	
Vascular disorders	Peripheral oedema, hypertension. flushing, hot flushes.		
Respiratory, thoracic and mediastinal	Chest pain, dyspnoea, cough, pharyngitis.	Bronchitis, sinusitis or rhinitis.	

disorders			
Gastrointestinal disorders	Constipation, dry mouth, gastrointestinal disturbances, including abdominal pain, diarrhoea, nausea or vomiting.		
Hepato-biliary disorders	Abnormalities in liver enzyme values, increases in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase.	Elevated gamma-GT and bilirubin, hepatitis.	
Skin and subcutaneous tissue disorders	Skin rash, sweating, hair thinning (alopecia), allergic reactions.	Pruritus, Erythema multiforme, Stevens-Johnson syndrome, angioedema, urticaria and anaphylaxis, cutaneous vasculitis (including some reports of Henoch-Schönlein purpura)**.	
Musculoskeletal and connective tissue disorders	Arthralgia/joint pain/stiffness, myalgia, back and bone pain, bone fractures, arthritis, osteoporosis.	Trigger finger.	
Reproductive system and breast disorders	Vaginal bleeding***, vaginal dryness.		
General	Asthenia, pain, pelvic pain.	Flu syndrome.	

disorders and administration site conditions			

* Events of Carpal Tunnel Syndrome have been reported in patients receiving TEVA ANASTROZOLE 1 mg 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 Less frequent based on the worst value of the point estimate.

***Vaginal bleeding has been reported frequently, mainly in patients with advanced breast cancer during the first few weeks after changing from existing hormonal therapy to treatment with TEVA ANASTROZOLE 1 mg. If bleeding persists, further evaluation should be considered.

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 TEVA ANASTROZOLE 1 mg 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 TEVA ANASTROZOLE 1 mg.

Adverse reactions identified during post-marketing experience:

System organ class	Side effects
Metabolism and nutrition disorders	Anorexia, hypercholesterolaemia, hypercalcaemia (with or without an increase in parathyroid hormone).

Nervous system disorders	Headache, carpal tunnel syndrome, somnolence, sensory disturbances (including paraesthesia, taste loss and taste perversion).
Vascular disorders	Hot flushes.
Gastrointestinal disorders	Nausea, diarrhoea, vomiting.
Hepato-biliary disorders	Increase in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase, increase in gamma-GT and bilirubin, hepatitis.
Skin and subcutaneous tissue disorders	Rash, hair thinning (alopecia), allergic reactions; urticaria, Erythema multiforme, anaphylactoid reaction, Stevens-Johnson syndrome, angioedema.
Musculoskeletal and connective tissue disorders	Arthralgia/joint stiffness, arthritis, bone pain, trigger finger, myalgia.
Reproductive system and breast disorders	Vaginal dryness, vaginal bleeding.
General disorders and administration site conditions	Asthenia.

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **6.04 Adverse Drug Reactions Reporting Form**, found online under SAHPRA's publications:

https://sahpra.org.za/wpcontent/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

4.9 Overdose:

Refer to side effects for possible symptoms of overdosage. There is limited clinical experience of accidental overdose. In animal studies, TEVA ANASTROZOLE 1 mg demonstrated low acute toxicity. Clinical trials have been conducted with various dosages of TEVA ANASTROZOLE 1 mg, 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 TEVA ANASTROZOLE 1 mg that results in life-threatening symptoms has not been established. 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. Emptying the stomach via induction of emesis if the patient is alert is recommended.

Haemodialysis may be helpful because TEVA ANASTROZOLE 1 mg 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:

5.1 Pharmacodynamic properties:

A 21.12 Hormone inhibitors.

Pharmacotherapeutic group: Enzyme inhibitors, ATC code: L02B G03

Mechanism of Action:

Anastrozole is a selective non-steroidal inhibitor of aromatase (oestrogen synthetase) system, which converts adrenal androgens to oestrogens in peripheral tissue. Anastrozole does not possess any progestogenic, androgenic or oestrogenic activity.

5.2 Pharmacokinetic properties:

Anastrozole is rapidly and almost completely absorbed from the gastrointestinal tract, maximum plasma concentrations typically occur within two hours of dosing. Food decreases the rate of absorption.

Anastrozole is eliminated slowly with a plasma elimination half-life of 40 to 50 hours. Anastrozole is only 40 % bound to plasma proteins. Anastrozole is metabolised in the liver, and excreted in urine (less than 10 % of the dose), mainly as metabolites. The terminal plasma elimination half-life is about 40 to 50 hours, and steady-state concentrations are achieved after about 7 days in patients receiving once-daily doses.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Tablet core:

lactose monohydrate

povidone

sodium starch glycolate

magnesium stearate

purified water

Film coating:

Opadry 02G28619 containing:

hypromellose 5cP 2910 (E464)

titanium dioxide (E171)

macrogol 6000

macrogol 400

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

3 years.

6.4 Special precautions for storage:

Store at or below 25 °C.

Do not remove blisters from carton until required for use.

6.5 Nature and contents of the container:

Transparent PVC/PVdC – Aluminium blister packs of 30 tablets. The blister strips together with a package insert are packaged into an outer cardboard carton.

6.6 Special precautions for disposal and other handling:

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

Gauteng

South Africa

2090

8. REGISTRATION NUMBERS:

42/21.12/0760

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTORISATION:

Date of registration: 07 December 2012

10. DATE OF THE REVISION OF THE TEXT:

14 October 2021