1.3.1.1 Professional Information for Medicines for Human Use

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CABREXID FILM-COATED TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CABREXID FILM-COATED TABLETS:

Each film-coated tablet contains 1 mg anastrozole.

Contains sugar: lactose monohydrate 91,00 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White, biconvex, film-coated tablet debossed with ‘A1’ on one side and plain 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

Posology

Adults including the elderly:

One 1 mg tablet to be taken orally once a day.

Special Population

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.

Elderly patients:

No specific dosage adjustments of CABREXID are recommended based on patient age.

Paediatric population:

The safety and efficacy of CABREXID in children under the age of 18 years has not been established

Not recommended for use in children.

Method of administration

CABREXID should be taken orally.

4.3. Contraindications

CABREXID is contraindicated in:

- patients with hypersensitivity to anastrazole or to any of the ingredients of CABREXID
- pre-menopausal women
- pregnant/lactating women

- 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

CABREXID should not be used in premenopausal women. 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 menopausal status. There are no data to support the use of CABREXID with LHRH analogues.

Co-administration of tamoxifen or oestrogen-containing therapies with CABREXID should be avoided as this may diminish its pharmacological action (see section 4.5 and 5.1).

Effect on bone mineral density

As CABREXID lowers circulating oestrogen levels it may cause a reduction in bone mineral density with a possible consequent increased risk of fracture (see section 4.8).

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 CABREXID in postmenopausal women and could be considered (see section 4.8).

Hepatic impairment

CABREXID 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 CABREXID in patients with moderate and severe hepatic impairment is contraindicated (see section 4.3).

Renal impairment

CABREXID 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, see section 5.2); in patients with severe renal impairment (creatinine clearance less than 20 mL/min), administration of CABREXID (see section 4.3).

Paediatric population

CABREXID 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).

CABREXID 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, CABREXID 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

CABREXID contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take CABREXID.

4.5. Interaction with other medicines and other forms of interaction

CABREXID 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 CABREXID 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 CABREXID who also received other commonly prescribed medicinal products. There were no clinically significant interactions with bisphosphonates (see section 5.1).

Co-administration of tamoxifen or oestrogen-containing therapies with CABREXID should be avoided as this may diminish its pharmacological action (see section 4.4 and 5.1).

4.6. Fertility, pregnancy and lactation

Pregnancy

CABREXID is contraindicated during pregnancy (see section 4.3).

There is no data from the use of CABREXID in pregnant women. Studies in animals have shown reproductive toxicity.

Breastfeeding

CABREXID is contraindicated during pregnancy (see section 4.3).

There is no data on the use of CABREXID during lactation.

Fertility

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

4.7. Effects on ability to drive and use machines

Asthenia and somnolence have been reported with the use of CABREXID 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 list of adverse reactions*

Frequency groupings are defined according to the following convention:

Frequent = more frequent, very common and common;

Less frequent = single report or isolated reports, uncommon, rare, very rare

Table 1: Adverse reactions by System Organ Class and frequency

System Organ Class	Frequency	Adverse reactions
Metabolism and nutrition disorders	Frequent	Anorexia, Hypercholesterolaemia
	Less frequent	Hypercalcaemia (with or without an increase in parathyroid hormone)

Nervous system disorders	Frequent	Headache, Somnolence, Carpal Tunnel Syndrome* , Sensory disturbances (including paraesthesia, taste loss and taste perversion)
Vascular disorders	Frequent	Hot flushes
Gastrointestinal disorders	Frequent	Nausea, Diarrhoea, Vomiting
Hepatobiliary disorders	Frequent	Increases in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase
	Less frequent	Increases in gamma-GT and bilirubin, Hepatitis
Skin and subcutaneous tissue disorders	Frequent	Rash, Hair thinning (alopecia), Allergic reactions

	Less frequent	Urticaria, Erythema multiforme, Anaphylactoid reaction, Cutaneous vasculitis (including some reports of Henoch-Schönlein purpura)** , Stevens-Johnson syndrome, Angioedema
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia/joint stiffness, Arthritis, Osteoporosis, Bone pain, Myalgia
	Less frequent	Trigger finger
Reproductive system and breast disorders	Frequent	Vaginal dryness, Vaginal bleeding ***
General disorders and administration site conditions	Frequent	Asthenia
*Events of Carpal Tunnel Syndrome have been reported in patients receiving CABREXID 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 Arimidex, Tamoxifen, Alone or in Combination) study,		

the frequency category for these events can be considered as 'Rare' (≥ 0,01 % and < 0,1 %) 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 CABREXID. If bleeding persists, further evaluation should be considered.

c. Description of selected adverse reactions

Cardiovascular events

In a study conducted in postmenapausal women with operable breast cancer treated for 5 years, ischaemic cardiovascular events were reported more frequently in patients treated with CABREXID 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 CABREXID

Bone fractures

Fracture rates of 22 per 1000 patient-years and 15 per 1000 patient-years were observed for the CABREXID and tamoxifen groups, respectively, after a median follow-up of 68 months. The observed fracture rate for CABREXID is similar to the range reported in age-matched postmenopausal populations. The incidence of osteoporosis was 10,5 % in patients treated with CABREXID and 7,3 % in patients treated with tamoxifen. It has not been determined whether the rates of fracture and osteoporosis seen in ATAC in patients on CABREXID treatment reflect a protective effect of tamoxifen, a specific effect of CABREXID, or both.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form'. Found under SAHPRA's publications: https://www/sahpra.org.za/Publications/Index/8

4.9. Overdose

Symptoms

There is limited clinical experience of accidental overdose. In animal studies, anastrozole demonstrated low acute toxicity. Clinical trials have been conducted with various dosages of CABREXID, 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 CABREXID that results in life-threatening symptoms has not been established. Refer to possible side effects in the case of an overdose.

Treatment

There is no specific antidote to overdose and treatment must be symptomatic. In the management of an overdose, consideration should be given to the possibility that multiple substances may have been taken. Dialysis may be helpful because CABREXID 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

Pharmacotherapeutic group: Enzyme inhibitors, ATC code: L02BG03

Mechanism of action

Anastrozole is a potent and highly selective non-steroidal aromatase inhibitor. In postmenopausal women, oestradiol is produced primarily from the conversion of androstenedione to oestrone through the aromatase enzyme complex in peripheral tissues. Oestrone is subsequently converted to oestradiol. Reducing circulating oestradiol 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 oestradiol suppression of greater than 80 % using a highly sensitive assay. Anastrozole does not possess any progestogenic, androgenic, or oestrogenic 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.

5.2. Pharmacokinetic properties

Absorption

Absorption of anastrozole is rapid and maximum plasma concentrations typically occur after two hours of dosing (under fasted conditions). Food decreases the rate but not the extent of absorption. The 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.

Biotransformation and Elimination

Anastrozole is eliminated slowly with a plasma elimination half-life of 40 to 50 hours. 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, the major metabolite in plasma, does not inhibit aromatase.

Special Populations

Renal impairment

The apparent clearance (CL/F) of anastrozole, following oral administration, was not altered in volunteers with severe renal impairment (GFR < 30mL/min), 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 iis contraindicated (see section 4.2 and 4.4).

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. In patients with moderate to severe hepatic impairment, anastrozole is contraindicated.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

CABREXID film-coated tablets contain the following inactive ingredients: Lactose monohydrate, sodium starch glycolate, Povidone K-30, magnesium stearate.

Coating material: MPMC 2910/Hypromellose, titanium dioxide (CI 77891), Macrogol/PEG

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 °C.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

30 film-coated tablets are packed in printed 25 micron aluminium foil / clear 25 micron PVC film blister pack. Each carton contains 3 blisters of 10 film-coated tablets each. The blisters are further packed in pre-printed cartons with leaflet.

6.6. Special precautions for disposal

No special requirements.

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

AUROGEN SA (Pty) Ltd

Woodhill Office Park, Building 1, First Floor

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

8. REGISTRATION NUMBER

54/21.12/0162

9. DATE OF FIRST AUTHORISATION

28 February 2023

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