SCHEDULING STATUS: **S4**

PROPRIETARY NAME AND DOSAGE FORM:

AROMASIN® 25mg (Tablets)

COMPOSITION:

Each sugar-coated tablet contains 25 mg exemestane.

Preservative: methyl p-hydroxybenzoate 0,003 % m/m.

PHARMACOLOGICAL CLASSIFICATION:

A 21.12 Hormone inhibitors

PHARMACOLOGICAL ACTION:

Pharmacodynamic Properties:

Exemestane is an irreversible, steroidal aromatase inhibitor, structurally related to the natural substrate androstenedione. In postmenopausal women, oestrogens are produced primarily from the conversion of androgens into oestrogens through the aromatase enzyme in peripheral tissues. Exemestane significantly lowered serum oestrogen concentrations starting from a 5 mg dose, reaching maximal suppression (>90 %) with a dose of 10 – 25 mg. In postmenopausal breast cancer patients treated with the 25 mg daily dose, whole body aromatization was reduced by 98 %. Exemestane does not possess any progestogenic or oestrogenic activity. A slight androgenic activity, probably due to the 17-hydro derivative, has been observed, mainly at high doses. In multiple daily dose trials, AROMASIN had no detectable effects on adrenal biosynthesis of cortisol or aldosterone, measured before or after ACTH challenge, thus demonstrating its selectivity with regard to the other

enzymes involved in the steroidogenic pathway.

A non dose-dependent slight increase in serum LH and FSH levels has been observed even at low doses.

Pharmacokinetic Properties:

Absorption: Following oral administration, exemestane is rapidly absorbed. Animal data suggest that the oral bioavailability could be incomplete due to first-pass metabolism. At a single dose of 25 mg given after a meal, average peak plasma levels of 18 ng/ml are achieved within 2 hours post-dosing. Food was shown to enhance absorption, resulting in plasma levels 40 % higher than those observed in subjects under fasting conditions.

Distribution: After the peak, plasma levels of exemestane decline in a polyexponential manner with a terminal half-life of approximately 24 hours. Exemestane is extensively distributed into tissues as reflected by a high volume of distribution. The plasma protein binding of exemestane is approximately 90 % and the fraction bound is independent from the total concentration. The distribution of the drug and/or its metabolites into blood cells is negligible.

Metabolism and excretion: No significant deviations from dose-proportional pharmacokinetics were observed in healthy volunteers up to a 50 mg oral dose. Following repeated daily administration of 25 mg, plasma concentrations of the unchanged drug were of a similar order to those measured after single dosing. Following oral administration of a single dose radiolabelled exemestane, the elimination of drug-related products was shown to be essentially complete within 1 week, with approximately equal proportions of the dose eliminated in urine and faeces. The amount of drug excreted unchanged in urine is less than 1 % of the dose. The clearance of exemestane is high, mainly due to metabolism. The biotransformation proceeds through oxidation of the methylene group at position 6 via the CYP

3A4 isoenzyme and/or reduction of 17-keto group by aldoketoreductases. Subsequently, many secondary metabolites are formed, each accounting for a limited amount of the drug. The metabolites are either inactive or less active than the parent drug in inhibiting aromatase.

Special populations:

Age: No significant correlation between the systemic exposure of exemestane and the age of subjects has been observed.

Renal insufficiency: exemestane pharmacokinetics have been investigated in subjects with severe renal insufficiency ($CL_{CR} \leq 30$ mL/min). In these subjects the systemic exposure of exemestane after a single dose was found to be approximately double that of healthy volunteers.

Hepatic insufficiency: exemestane pharmacokinetics have been investigated in subjects with moderate and severe hepatic insufficiency. The systemic exposure to AROMASIN was 2 – 3 times higher than in healthy volunteers.

INDICATIONS:

Aromasin is indicated for the following:

- Treatment of advanced oestrogen receptor positive breast cancer in women with natural or induced postmenopausal status whose disease has progressed following anti-oestrogen therapy.
- Adjuvant treatment of postmenopausal women with oestrogen receptor positive invasive early breast cancer who are disease free, following at least 2 years of initial adjuvant tamoxifen therapy.

CONTRA-INDICATIONS:

AROMASIN tablets are contra-indicated in patients with a known hypersensitivity to exemestane or to any of the excipients, in pre-menopausal women and in pregnant or lactating women.

WARNINGS AND SPECIAL PRECAUTIONS:

Effects on ability to drive and use machines:

Drowsiness, somnolence, asthenia and dizziness have been reported with the use of the medicine. Patients should be advised that, if these events occur, their physical and/or mental abilities required for operating machinery or driving a car may be impaired.

Due to its mode of action, Aromasin should not be administered to pre-menopausal women.

Therefore, the postmenopausal status should be ascertained by assessment of LH, FSH and oestradiol levels.

Aromasin should not be co-administered with oestrogen-containing medicines as these would negate its pharmacological action.

During adjuvant treatment with Aromasin, women with osteoporosis or at risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry at the commencement of treatment and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored.

INTERACTIONS:

In vitro evidence showed that the exemestane is metabolised through cytochrome P450 (CYP) 3A4 and aldoketoreductases and does not inhibit any of the major CYP isoenzymes. In a clinical

pharmacokinetic study, the specific inhibition of CYP 3A4 by ketoconazole showed no significant effects on the pharmacokinetics of Aromasin.

In a pharmacokinetic interaction study with rifampicin, a potent CYP 3A4 inducer, the pharmacologic activity (i.e. oestrogen suppression) was not affected, despite an about 50% decrease in the C_{max} and AUC of exemestane.

PREGNANCY AND LACTATION:

AROMASIN is contra-indicated in pregnant or lactating women. If AROMASIN is taken accidentally, administration should be immediately discontinued.

DOSAGE AND DIRECTIONS FOR USE:

Adults and elderly patients:

The recommended dose of AROMASIN is one 25 mg tablet to be taken once daily, preferably after a meal.

In patients with:

- Advanced breast cancer, treatment with AROMASIN should continue until tumour progression is evident.
- Early breast cancer, treatment with Aromasin should continue until completion of five years of adjuvant hormonal therapy (anti-oestrogen followed by Aromasin), or until tumour relapse occurs.

No dose adjustments are required for patients with hepatic or renal insufficiency.

Children:

Not recommended for use in children.

SIDE-EFFECTS:

In the clinical studies conducted with Aromasin, the discontinuation rate due to adverse events was 2,8 % in the overall patient population with advanced breast cancer receiving the standard dose of 25 mg and 6,3% in patients with early breast cancer receiving adjuvant treatment with Aromasin following initial adjuvant tamoxifen therapy.

In patients with early breast cancer, the most commonly reported adverse reactions were hot flushes (21%) and fatigue (16%).

Most adverse reactions can be attributed to the normal pharmacological consequences of oestrogen deprivation (e.g. hot flushes).

The side-effects were categorized utilizing the incidence rate as follows:

Very Common: >1/10 (>10%)

Common: >1/100 and ≤1/10 (>1% and ≤10%)

Uncommon: >1/1000 and ≤1/100 (>0,1% and ≤1%)

Rare: >1/10 000 and ≤1/1000 (>0,01% and ≤0,1%)

System Organ Class	***Frequency***	***Adverse Events***
Metabolism and nutrition disorders	Common	Anorexia
Psychiatric disorders	Very Common	Insomnia
	Common	Depression

System Organ Class	***Frequency***	***Adverse Events***
Nervous system disorders	Very Common	Headache
	Common	Dizziness, carpal tunnel syndrome
	Uncommon	Somnolence
Vascular disorders	Very common	Hot flushes
Gastrointestinal disorders	Very Common	Nausea
	Common	Abdominal pain, vomiting, constipation, dyspepsia, diarrhoea
Skin and subcutaneous tissue disorders	Very Common	Increased sweating
	Common	Rash, alopecia
Musculoskeletal and bone disorders	Common	Joint and musculoskeletal pain
General disorders and administration site conditions	Very Common	Fatigue
	Common	Pain, peripheral oedema

System Organ Class	***Frequency***	***Adverse Events***
	Uncommon	Asthenia

Blood and lymphatic system disorders

In patients with Advanced Breast Cancer, thrombocytopenia and leucopenia have been rarely reported. An occasional decrease in lymphocytes has been observed in approximately 20 % of patients receiving Aromasin, particularly in patients with pre-existing lymphopenia; however, mean lymphocyte values in these patients did not change significantly over time. This effect has not been observed in patients treated for early breast cancer.

Hepatobiliary disorders

Elevations of liver enzymes have been observed. Elevation of alkaline phosphatase and bilirubin was very commonly observed, although usually not associated with elevation of liver enzymes.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Clinical trials have been conducted with Aromasin given up to 800 mg in a single dose to healthy female volunteers and up to 600 mg daily to postmenopausal women with advanced breast cancer; these dosages were well tolerated. The single dose of Aromasin that could result in life-threatening symptoms is not known. In rats and dogs, lethality was observed after single oral doses equivalent to 2000 and 4000 times, respectively, the recommended human dose on a mg/m^2 basis.

There is no specific antidote to overdosage and treatment must be symptomatic. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

IDENTIFICATION:

Round, biconvex, off-white to slightly greyish sugar-coated tablets, printed with number 7663 on one side in black ink.

PRESENTATION:

Blister packs of 30.

STORAGE INSTRUCTIONS:

Store below 30 °C. Keep out of reach of children.

REGISTRATION NUMBER:

35/21.12/0011

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd.

85 Bute Lane

Sandton

2196

South Africa

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