PROPOSED PROFESSSIONAL INFORMATION (CLEAN COPY)

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ACTAMASIN 25 (film coated tablets)

Strength: Each tablet contains 25 mg exemestane.

Pharmaceutical form: Film coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative declaration: Exemestane.

Quantitative composition: Each film coated tablet contains 25 mg exemestane.

Excipients with known effect: Mannitol 0.9040 mg

For the full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Film coated tablet.

A white to off-white, round, biconvex film coated tablet, debossed with 'E25' on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ACTAMASIN 25 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.

4.2 Posology and method of administration:

Posology:

Adults and elderly patients:

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

In patients with:

• Advanced breast cancer, treatment with ACTAMASIN 25 should continue until tumour progression is evident.

• Early breast cancer, treatment with ACTAMASIN 25 should continue until completion of five years of adjuvant hormonal therapy (anti-oestrogen followed by ACTAMASIN 25), or until tumour relapse occurs.

No dose adjustments are required for patients with hepatic or renal insufficiency (see section 5.2).

Paediatric population

Not recommended for use in children.

Method of administration:

Adults and elderly patients:

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

In patients with:

- Advanced breast cancer, treatment with ACTAMASIN 25 should continue until tumour progression is evident.
- Early breast cancer, treatment with ACTAMASIN 25 should continue until completion of five years of adjuvant hormonal therapy (anti-oestrogen followed by ACTAMASIN 25), or until tumour relapse occurs.

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

Children:

Not recommended for use in children.

4.3 Contraindications

ACTAMASIN 25 tablets are contraindicated in:

- Patients with hypersensitivity to exemestane or to any of the excipients listed in section 6.1.
- Pre-menopausal women
- Pregnant or lactating women (see section 4.6)

4.4 Special warnings and precautions for use

Due to its mode of action, ACTAMASIN 25 should not be administered to women with pre-menopausal endocrine status. Therefore, whenever clinically appropriate, the post-menopausal status should be ascertained by assessment of LH, FSH and oestradiol levels.

ACTAMASIN 25 should be used with caution in patients with hepatic or renal impairment.

ACTAMASIN 25 is a potent oestrogen lowering medicine, and a reduction in bone mineral density (BMD) and an increased fracture rate have been observed following administration (see section 5.1).

Routine assessment of 25 hydroxy vitamin D levels prior to the start of aromatase inhibitor treatment should be considered, due to the high prevalence of severe deficiency in women with early breast cancer. Women with Vitamin D deficiency should receive supplementation with Vitamin D.

During adjuvant treatment with ACTAMASIN 25, 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.

ACTAMASIN 25 contains mannitol, which may have a mild laxative effect.

4.5 Interaction with other medicines and other forms of interaction

In vitro evidence showed that the exemestane is metabolised through cytochrome P450 (CYP)3A4 and aldoketoreductases (see section 5.2) 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 exemestane.

In an interaction study with rifampicin, a potent CYP450 inducer, at a dose of 600 mg daily and a single dose of exemestane 25 mg, the AUC and C_{max} of exemestane was reduced. Since the clinical relevance of this interaction has not been evaluated, the co-administration of medicinal products, such as rifampicin, anticonvulsants (e.g. phenytoin and carbamazepine) and herbal preparations containing Hypericum perforatum (St John's Wort) known to induce CYP3A4 may reduce the efficacy of ACTAMASIN 25.
ACTAMASIN 25 should be used cautiously with medicinal products that are metabolised via CYP3A4 and have a narrow therapeutic window. There is no clinical experience of the concomitant use of ACTAMASIN 25 with other anticancer medicines.
ACTAMASIN 25 should not be co-administered with oestrogen-containing medicines as these would negate its pharmacological action.

4.6 Fertility, Pregnancy and lactation

Women of perimenopausal status or child-bearing potential.

The medical practitioner needs to discuss the necessity of adequate contraception with women who have the potential to become pregnant including women who are perimenopausal or who have recently become postmenopausal, until their postmenopausal status is fully established (see sections 4.3 and 4.4).

Pregnancy

No clinical data on exposed pregnancies are available with exemestane as in ACTAMASIN 25.
ACTAMASIN 25 is contra-indicated in pregnant. If ACTAMASIN 25 is taken accidentally, administration should be immediately discontinued.

Breast-feeding

It is not known whether exemestane is excreted into human milk. ACTAMASIN 25 is contra-indicated in lactating women (see section 4.3).

4.7 Effects on ability to drive and use machines

Drowsiness, somnolence, asthenia and dizziness have been reported with the use of ACTAMASIN 25. 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.

4.8 Undesirable effects

ACTAMASIN 25 is generally well tolerated at a standard dose of 25 mg/day, and undesirable effects were usually mild to moderate.

The most frequently recorded adverse reactions during studies in patients with early breast cancer receiving adjuvant treatment with exemestane, following initial adjuvant tamoxifen therapy, was hot flushes, arthralgia and fatigue, compared to hot flushes and nausea in patients with advanced breast cancer.

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

Blood and lymphatic system disorders:

Less Frequent: Leucopenia, thrombocytopenia, lymphocytopoenia.

Frequency not known: Lymphocyte count decreased

Immune system disorders:

Less frequent: Hypersensitivity

Metabolism and nutrition disorders:

Frequent: Anorexia

Psychiatric disorders:

Frequent: Insomnia, depression

Nervous system disorders:

Frequent: Headache, dizziness, paraesthesia, carpal tunnel syndrome.

Less frequent: Somnolence

Vascular disorders:

Frequent: Hot flushes

Gastrointestinal disorders:

Frequent: Nausea, abdominal pain, vomiting, constipation, dyspepsia, diarrhoea.

Hepato-biliary disorders:

Frequent: Hepatic enzyme increased, blood bilirubin increased, blood alkaline phosphatase increased

Less frequent: Hepatitis, cholestatic hepatitis

Skin and subcutaneous tissue disorders:

Frequent: Increased sweating, rash, alopecia, urticaria, pruritus

Less frequent: Acute generalised exanthematous pustulosis

Musculoskeletal and bone disorders:

Frequent: Joint and musculoskeletal pain, fractures, osteoporosis

General disorders and administration site conditions:

Frequent: Fatigue, pain, peripheral oedema

Less frequent: Asthenia

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 Reactions Reporting Form", found online under SAHPRA's publications:

https://sahpra.org.za/Publications/Index/8

4.9 Overdose

Clinical trials have been conducted with exemestane as in ACTAMASIN 25 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 ACTAMASIN 25 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.

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Steroidal aromatase inhibitor; anti-neoplastic agent

ATC: L02BG06

A21.12 Hormone inhibitors

5.1 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, exemestane 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.

5.2 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 elimination: 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 has been investigated in subjects with severe renal insufficiency (CLCR < 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 has been investigated in subjects with moderate and severe hepatic insufficiency. The systemic exposure to ACTAMASIN 25 was 2 – 3 times higher than in healthy volunteers.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica, crospovidone, hypromellose, macrogol, magnesium stearate, mannitol, microcrystalline cellulose, polysorbate, sodium starch glycolate, and titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C. Protect form light.

Keep the blister in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

A white to off-white, round, biconvex film coated tablet, debossed with 'E25' on one side and plain on the other.

White opaque PVC/PVdC-Aluminium blister strips containing 10 tablets each. Each cardboard carton contains 30 tablets.

6.6 Special precautions for disposal and other handling

This medicine does not require any special storage conditions.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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PROPOSED PROFESSSIONAL INFORMATION (CLEAN COPY)

8. REGISTRATION NUMBER

47/21.12/1118

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 June 2021

10. DATE OF REVISION OF THE TEXT

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