SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

EQUISIN film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 25 mg exemestane.

Contains sugar (mannitol, 40,40 mg per tablet).

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets

White to off-white, round compound cup film-coated tablet with “25” on one side and plain on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

EQUISIN 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 is one EQUISIN 25 mg tablet to be taken once daily, preferably after a meal.

In patients with:

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

For patients with mild hepatic or mild renal insufficiency no dose adjustments are required.

Paediatric population

Not recommended for use in children.

Method of administration

For oral use.

4.3 Contraindications

EQUISIN is contraindicated in:

- Patients with a known hypersensitivity to exemestane or to any of the excipients listed in section 6.1.
- Pre-menopausal women.
- Pregnant or lactating women.

4.4 Special warnings and precautions for use

Reductions in bone mineral density can occur with long-term use of EQUISIN and an increased fracture rate have been observed following administration with EQUISIN. Density should therefore be assessed at the start of therapy and patients monitored during therapy.

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

carefully monitored.

EQUISIN should not be administered to pre-menopausal women. The postmenopausal status should be ascertained by assessment of LH, FSH and oestradiol levels.

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

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

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium free".

4.5 Interaction with other medicines and other forms of interaction

EQUISIN is metabolised by aldoketoreductases and the cytochrome P450 isoenzyme CYP3A4. It does not inhibit any of the major CYP isoenzymes.

Significant effects on the pharmacokinetics of EQUISIN by cytochrome P450 isoenzyme inhibitors are considered unlikely.

Plasma concentration and efficacy of EQUISIN may be reduced if given concomitantly with inducers of CYP isoenzymes such as rifampicin, phenytoin, carbamazepine, or herbal preparations containing *hypericum perforatum* (St. John's Wort). EQUISIN should be used cautiously with medicines that are substrates for CYP3A4 and that have a narrow therapeutic index.

EQUISIN should not be given with oestrogen-containing medicines as these would negate its pharmacological action.

4.6 Fertility, pregnancy and lactation

Women of childbearing 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

EQUISIN is contraindicated in pregnant women. If it is taken accidentally, administration should be discontinued immediately.

Breastfeeding

EQUISIN is contraindicated in lactating women.

4.7 Effects on ability to drive and use machines

Somnolence, dizziness, drowsiness and asthenia have been reported with the use of EQUISIN. Patients should be advised that their ability to drive, operate dangerous machinery or perform potentially hazardous tasks may be impaired.

4.8 Undesirable effects

a) Summary of the safety profile

The most frequently reported adverse reactions were hot flushes, arthralgia, fatigue and nausea.

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

b) Tabulated summary of adverse reactions

MedDRA System Organ Class	**Frequent**	**Less frequent**	**Frequency unknown**
Infections and infestations			Infection, upper respiratory tract infection, urinary tract

			infection, influenza-like symptoms
Immune system disorders		Hypersensitivity	
Blood and lymphatic system disorders	Thrombocytopenia**, leukopenia**		Lymphocyte count decreased**
Metabolism and nutrition disorders	Anorexia		
Psychiatric disorders	Insomnia, depression, anxiety, confusion		
Nervous system disorders	Headache, dizziness, carpal tunnel syndrome, paraesthesia	Somnolence	
Vascular disorders	Hot flushes, hypertension, lymphoedema		
Respiratory, thoracic and mediastinal disorders			Dyspnoea, bronchitis, chest pain, sinusitis, pharyngitis, rhinitis
Gastrointestinal disorders	Nausea, abdominal pain, vomiting, constipation, dyspepsia, diarrhoea		
Hepato-biliary disorders		Hepatitis†, cholestatic jaundice †	
Skin and subcutaneous tissue disorders	Hyperhidrosis, rash, alopecia, pruritus, urticaria	Acute generalised exanthematous pustulosis†	
Musculoskeletal and	Joint and		

bone disorders	musculoskeletal pain,* osteoporosis, fracture		
General disorders and administration site conditions	Fatigue, pain, peripheral oedema, asthenia		
Investigations:	Hepatic enzyme increase, blood bilirubin increased, blood alkaline phosphatase increase		

***** Includes: arthralgia, and less frequently pain in extremity, osteoarthritis, back pain, arthritis, myalgia and joint stiffness.

****** In patients with advanced breast cancer thrombocytopenia and leukopenia have been less frequently reported. An occasional decrease in lymphocytes has been observed in approximately 20 % of patients receiving EQUISIN, particularly in patients with pre-existing lymphopenia; however, mean lymphocyte values in these patients did not change significantly over time and no corresponding increase in viral infections was observed. It has been reported that these effects have not been observed in patients treated in early breast cancer studies.

† Frequency calculated by rule of 3/X.

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 Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

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

5.1 Pharmacodynamic properties

A 21.12 – Hormone inhibitors.

L02 ENDOCRINE THERAPY, Hormone antagonists and related agents, Aromatase Inhibitors

ATC code: L02BG06

Exemestane is a type I steroidal aromatase inhibitor and an analogue of the natural substrate adrostenedione. Exemestane lowers serum oestrogen levels by irreversibly inactivating peripheral tissue aromatase enzyme, the enzyme responsible for converting androgens into oestrogens in postmenopausal women.

At a 25 mg daily dose, exemestane inhibits aromatase activity by 98 % and lowers plasma oestrone and oestradiol levels by about 90 %.

Exemestane does not possess any oestrogenic or progestogenic activity. A slight androgenic activity has been observed, mainly at high doses. It has no detectable effects on adrenal biosynthesis of cortisol or aldosterone.

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

5.2 Pharmacokinetic properties

Absorption:

Exemestane is rapidly absorbed from the gastrointestinal tract. The bioavailability of exemestane is limited by first-pass metabolism, but food was shown to enhance absorption, resulting in 40 % higher plasma levels compared to those observed in fasting conditions.

Distribution:

Exemestane is extensively bound (90 %) to plasma proteins and widely distributed into tissues. It has a terminal elimination half-life of approximately 24 hours.

Biotransformation:

Exemestane is metabolised via oxidation by the cytochrome P450 isoenzyme CYP3A4 and/or via reduction by aldoketoreductases. The metabolites are either inactive or less active than the parent agent in inhibiting

aromatase.

Elimination:

Metabolites are excreted in urine and faeces, and less than 1 % of a dose is excreted unchanged in the urine.

Special populations:

Age:

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

Renal insufficiency:

In severe renal insufficiency, the systemic exposure of exemestane after a single dose is approximately double that of subjects with normal renal function.

Hepatic insufficiency:

The systemic exposure to exemestane is 2 – 3 times higher in subjects with moderate to severe hepatic insufficiency.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Copovidone type A

Colloidal anhydrous silica

Crospovidone type A

Mannitol

Magnesium stearate

Microcrystalline cellulose

Sodium starch glycolate

The coating consists of:

Hypromellose

Macrogol 400

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

PVC-PVdC/Aluminium blister strips with 10, 14, 20, 28, 30, 60 and 100 tablets per outer carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd.

100 Sovereign Road, Route 21 Corporate Park

Nellmapius Drive

Irene, Gauteng

0157

South Africa

8 REGISTRATION NUMBER

45/21.12/0908

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of Registration: 19 October 2013

10 DATE OF REVISION OF THE TEXT

10 July 2023