SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

KESSAR® 20 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 mg tablet contains tamoxifen citrate equivalent to 20 mg tamoxifen.

Contains sugar.

Excipients with known effect

Each KESSAR 20 mg tablet contains 103,1 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

KESSAR 20: White, round, convex, uncoated tablet, 9 mm in diameter embossed with "20" on the one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Therapy for advanced disease

KESSAR is indicated for advanced breast cancers that are estrogen receptor positive HER2.

Adjuvant therapy

KESSAR is effective in delaying recurrence following total mastectomy and axillary dissection or segmented mastectomy, axillary dissection and breast irradiation in women with axillary node-negative breast cancer where the cancer is estrogen receptor positive (HER2).

Data are insufficient to predict which women are most likely to benefit and to determine if KESSAR provides any benefit in women with tumours of less than 1 cm. In some adjuvant studies most of the benefit to date has been in the subgroup with 4 or more positive axillary nodes.

4.2 Posology and method of administration

Posology

The recommended daily dose is 20 mg given in 2 divided doses or as a single daily dose. Doses of up to 40 mg daily may be given but no additional benefit has been demonstrated. A response is usually not achieved until after a treatment period of 2 to 3 months.

In the management of advanced disease, KESSAR treatment is to be continued until disease progression.

The optimum duration of adjuvant therapy has not been established, but at least 2 years of treatment is advisable. However, recent data seem to suggest that no further therapeutic advantage is gained if the treatment is prolonged beyond 5 years.

Method of administration

For oral use.

4.3 Contraindications

- KESSAR is contraindicated in patients with known hypersensitivity to the active substance (tamoxifen) or any of the excipients (listed in section 6.1).

- KESSAR must not be given during pregnancy or to breastfeeding women and should be used with caution in women with functioning ovaries (see section 4.6).

4.4 Special warnings and precautions for use

An increased incidence of endometrial changes including hyperplasia, polyps, cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours), has been reported in association with KESSAR treatment. The underlying mechanism is unknown but may be related to the estrogen-like effect of KESSAR. Any patient receiving or having previously received KESSAR who report abnormal gynaecological symptoms, especially vaginal bleeding, or who presents with menstrual irregularities, vaginal discharge and symptoms such as pelvic pain or pressure should be promptly investigated.

There is evidence that treatment with KESSAR may increase the risk of thromboembolic events, including stroke, deep vein thrombosis and pulmonary embolism. In patients with breast cancer, prescribers should obtain careful histories with respect to the patient's personal and family history of venous thromboembolism. Patients should be advised to seek immediate medical attention if they become aware of any symptoms of thromboembolic events; in such cases, KESSAR should be stopped and appropriate anti-thrombosis measures initiated.

Co-administration with cytotoxic medicines increases the risk for thromboembolic events (see section 4.5).

KESSAR should be used cautiously in patients with existing leukopenia or thrombocytopenia. Periodic complete blood counts, including platelet counts, may be appropriate.

In pre-menopausal women, KESSAR completely suppresses menstruation and cystic ovarian swelling may develop.

Pre-menopausal patients must be examined before treatment to exclude the possibility of pregnancy. Moreover, KESSAR may increase estradiol plasma concentrations and may induce ovulation, exposing patients to risk of pregnancy.

Changes in calcium metabolism

Hypercalcaemia may occur in some breast cancer patients with bone metastases within a few weeks of starting treatment with KESSAR. Patients with bone metastases should be closely monitored during the first weeks of therapy. If hypercalcaemia does occur, appropriate measures should be taken and KESSAR should be discontinued. Serum calcium should be checked regularly.

When starting KESSAR therapy the patient should undergo an ophthalmological examination. Visual disturbances including corneal changes, cataracts and retinopathy have been reported in patients receiving KESSAR. Repeated ophthalmologic examination is essential in patients receiving KESSAR treatment. If visual changes (cataracts and retinopathy) occur while on KESSAR therapy, urgent ophthalmological investigation is necessary. Ocular adverse reactions may not be reversible after KESSAR discontinuation.

A number of secondary primary tumours, occurring at sites other than the endometrium and the opposite breast, have been reported in clinical trials following the treatment of breast cancer patients with KESSAR.

During treatment, periodic check-ups including gynaecological examination focusing on endometrial changes are recommended. These check-ups should be of a frequency and nature that is adapted to the individual woman and modified according to her clinical needs.

Hepato-carcinogenicity of KESSAR has been reported in long-term carcinogenicity studies with rodents. Cases of hepatocellular carcinoma have also been reported in clinical KESSAR studies.

Tamoxifen was shown to be genotoxic in some *in vivo* genotoxicity tests in rodents. Gonadal tumours in mice, and liver tumours in rats receiving tamoxifen, have been reported in long-term studies.

There are also study results suggesting an increased incidence of gastrointestinal cancers in association with KESSAR treatment in breast cancer patients. Liver laboratory values of patients on KESSAR treatment should be regularly monitored.

Assessment of triglycerides in serum may also be advisable.

It is recommended that the use of KESSAR as adjuvant therapy be limited to a maximum of 5 years for women with node-negative, estrogen receptor-positive breast cancers who have had lumpectomy or mastectomy and radiation treatment.

CYP2D6 polymorphism and CYP2D6 genotype

CYP2D6 polymorphism status may be associated with variability in clinical response to KESSAR. The poor metaboliser status may be associated with reduced response. The consequences of the findings for the treatment of CYP2D6 poor metabolisers have not been fully elucidated (see section 4.5 and 5.2).

Available clinical data suggest that patients who are homozygote for non-functional CYP2D6 alleles, may experience reduced effect of KESSAR (see section 5.2).

In the literature it has been shown that CYP2D6 poor metabolisers have a lowered plasma level of endoxifen, one of the most important active metabolites of KESSAR (see section 5.2).

Concomitant medicines that inhibit CYP2D6 may lead to reduced concentrations of the active metabolite endoxifen. Therefore, potent inhibitors of CYP2D6 (e.g. paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should whenever possible be avoided during KESSAR treatment (see section 4.5 and 5.2).

KESSAR contains lactose

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

4.5 Interaction with other medicines and other forms of interaction

When KESSAR is used concurrently with warfarin, a significant increase in the anticoagulant effect may occur leading to bleeding risks. KESSAR and warfarin should be used concomitantly with caution, and under these conditions the INR (International Normalised Ratio) should be closely monitored.

Platelet aggregation inhibitors should not be combined with KESSAR in order to avoid bleeding during the possible thrombocytopenic period.

The use of KESSAR in combination with aromatase inhibitors (such as anastrozole) as adjuvant therapy has not shown improved efficacy compared with KESSAR alone.

Hormone preparations, particularly estrogens (e.g. oral contraceptives) should not be combined with KESSAR because a mutual decrease in effect is possible.

Medicines which decrease renal calcium excretion (e.g. thiazide diuretics) may increase the risk of hypercalcaemia and should be used with caution in patients with bone metastases and who are receiving KESSAR.

There are two case reports where concomitant use of KESSAR and tegafur was observed to induce chronic active hepatitis and liver cirrhosis.

Co-administration with cytotoxic medicines increases the risk for thromboembolic events (see section 4.4).

Concomitant use of mitomycin (even in small doses) and KESSAR increases the risk for haemolytic-uraemic syndrome, anaemia and thrombocytopenia. Concomitant use should be avoided.

KESSAR is mainly metabolised by CYP3A4. Caution is required when co-administered with known inhibitors or inducers (such as rifampicin) of CYP3A4 enzymes. Pharmacokinetic interaction with CYP2D6 inhibitors, showing a 65 - 75 % reduction in plasma level of one or more active forms of the medicine, viz. endoxifen, has been reported in the literature.

Reduced efficacy of KESSAR has been reported with concomitant usage of some SSRI antidepressants (e.g. paroxetine) in some studies. Co-administration of KESSAR with potent CYP2D6 inhibitors (e.g. paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should whenever possible be avoided (see sections 4.4 and 5.2).

The serum levels of KESSAR and its metabolites are markedly reduced after aminoglutethimide administration due to increased tamoxifen clearance.

Concurrent use of bromocriptine may result in increased serum levels of KESSAR and its metabolites.

Various degrees of estrogen effects on Papanicolau ('Pap') smears have been reported in postmenopausal patients who are receiving KESSAR.

Increased serum thyroxine levels, likely due to an increase in thyroxine-binding globulin, may occur in patients who are receiving KESSAR, but are not accompanied by clinical hyperthyroidism.

4.6 Fertility, pregnancy and lactation

KESSAR is contraindicated in pregnancy and lactation (see section 4.3).

Women of childbearing potential / Contraception in males and females

Women of childbearing potential should not receive KESSAR until pregnancy is excluded and should use an effective barrier or other non-hormonal method of contraception during KESSAR therapy and for at least two months after discontinuation of KESSAR treatment.

Pregnancy

Tamoxifen was genotoxic in some *in-vitro* and *in-vivo* genotoxicity tests in rodents. In humans, foetal deaths, spontaneous abortions and birth defects have been reported in patients receiving KESSAR.

If the patient becomes pregnant (while receiving or after discontinuation of KESSAR), information on the potential hazard to the foetus should be provided.

Breastfeeding

Tamoxifen inhibits lactation in humans and no rebound lactation was observed after completion of therapy. Because of the potential hazard to nursing infants, breastfeeding is contraindicated during KESSAR treatment (see section 4.3).

4.7 Effects on ability to drive and use machines

Visual disturbances and fatigue have been observed with the use of KESSAR; caution is advised when driving or using machines.

4.8 Undesirable effects

Severe adverse reactions may be sometimes controlled by a reduction in dosage without loss of control of the disease.

Tabulated summary of adverse reactions

Very common: (≥ 1/10); common: (≥ 1/100 to < 1/10); uncommon: (≥ 1/1 000 to < 1/100); rare: (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000).

System organ class	**Frequency**	**Adverse effect**
Neoplasms benign malignant	Frequent	Uterine fibroids, endometrial cancer

and unspecified (including cysts and polyps)	Less frequent	Uterine sarcoma (mostly malignant mixed Mullerian tumours), tumour flare
	Unknown	Hepatocellular cancer
Blood and lymphatic system disorders	Frequent	Anaemia
	Less frequent	Thrombocytopenia, leukopenia, neutropenia, agranulocytosis, haemorrhagic episodes
Immune system disorders	Frequent	Hypersensitivity reactions (including urticaria, angioedema and dyspnoea)
Metabolism and nutrition disorders	More frequent	Fluid retention
	Less frequent	Hypercalcaemia (in patients with bony metastases)
	Unknown	Anorexia
Psychiatric disorders	Unknown	Depression, confusion
Nervous system disorders	Frequent	Ischaemic cerebrovascular events, stroke, headache, light-headedness, sensory disturbances (including paraesthesia and dysgeusia)
	Unknown	Cerebrovascular accidents, dizziness
Eye disorders	Frequent	Cataracts,

		retinopathy
	Less frequent	Visual disturbances (including blurred vision and loss of visual acuity), optic neuritis, corneal changes (including corneal opacities), optic neuropathy
Vascular disorders	More frequent	Hot flushes
	Frequent	Thromboembolic events (including deep vein thrombosis, microvascular thrombosis and pulmonary embolism)
	Unknown	Thrombophlebitis and thromboembolism
Respiratory, thoracic and mediastinal disorders	Less frequent	Interstitial pneumonitis
	Unknown	Cough
Gastrointestinal disorders	More frequent	Nausea
	Frequent	Vomiting, diarrhoea, constipation
	Less frequent	Pancreatitis
	Unknown	Abdominal cramps
Hepato-biliary disorders	Frequent	Changes in liver enzymes, fatty liver

	Less frequent	Cirrhosis of the liver, hepatitis, cholestasis, hepatic failure, hepatocellular injury, hepatic necrosis
Skin and subcutaneous tissue disorders	More frequent	Skin rash
	Frequent	Alopecia, dry skin
	Less frequent	Angioedema, Stevens-Johnson syndrome, cutaneous vasculitis, bullous pemphigoid,
		erythema multiforme, cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Frequent	Leg cramps, myalgia
Reproductive system and breast disorders	More frequent	Vaginal bleeding, vaginal discharge
	Frequent	Pruritus vulvae, endometrial changes (including hyperplasia and polyps), menstrual irregularities (including amenorrhoea) in pre-menopausal patients
	Less frequent	Endometriosis,

		cystic ovarian swelling, vaginal polyps
Congenital, familial and genetic disorders	Less frequent	Porphyria cutanea tarda
General disorders and administration site conditions	More frequent	Fatigue
	Unknown	Oedema, severe increase in bone and tumour pain
Investigations	Frequent	Hypertriglyceridaemia
	Unknown	Weight gain
Injury, poisoning and procedural complications	Less frequent	Radiation recall

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

On theoretical grounds, overdosage would be expected to cause enhancement of anti-estrogenic adverse reactions.

There have been reports in the literature that KESSAR given at several times the standard dose may be associated with prolongation of the QT interval of the ECG.

There is no specific antidote and treatment must be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.12 Hormone inhibitors

Mechanism of action

Tamoxifen exhibits anti- estrogenic activity by competing with estrogen for binding sites in the target organs. When bound to the receptor, tamoxifen induces changes in the receptor shape inhibiting its binding to the estrogen responsive element on DNA.

Tamoxifen also has weak estrogenic effects.

CYP2D6 polymorphism and CYP2D6 genotype: See section 4.4.

5.2 Pharmacokinetic properties

Absorption

After oral administration, tamoxifen is absorbed with maximum serum concentrations attained within 4 to 7 hours.

Distribution

Tamoxifen is highly protein bound to serum albumin (> 99 %). Steady state concentrations (about 300 ng/mL) are achieved after 4 weeks of treatment with 40 mg daily.

Metabolism

Tamoxifen is metabolised mainly via CYP3A4 to N-desmethyl-tamoxifen which is further metabolised by CYP2D6 to another active metabolite endoxifen. In patients who lack the enzyme CYP2D6, endoxifen concentrations are approximately 75 % lower than in patients with normal CYP2D6 activity. Administration of strong CYP2D6 inhibitors reduces endoxifen circulating levels to a similar extent.

Elimination

Excretion occurs primarily via the faeces and an elimination half-life of approximately 7 days has been calculated for the medicine itself, whereas the half-life of N-desmethyl-tamoxifen, the principal circulating metabolite, is 14 days.

Tamoxifen and/or its metabolites undergo extensive entero-hepatic circulation which can be accountable for prolongation of serum levels and primary faecal excretion.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, magnesium stearate, maize starch, povidone, and sodium starch glycolate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C and protect from light.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blister packs of 10 tablets in 30's and/or 250's.

40 ml high density polyethylene (HDPE) jar containing 30 tablets, closed with a 32 mm tamper-evident HDPE closure

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

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Sandton 2196

South Africa

Tel: +27 (0)11) 320 6000/0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBERS

KESSAR 20: S/21.12/359

9. DATE OF FIRST AUTHORISATION

KESSAR 20: 12 February 1986

10. DATE OF REVISION OF THE TEXT

10 June 2021

NAMIBIA: S2 KESSAR 20: Reg. No. 90/21.12/001322

BOTSWANA: S2 KESSAR 20: Reg. No. B9320920