SCHEDULING STATUS:

S4

PROPRIETARY NAMES (and dosage forms):

KESSAR® 20 (tablets)

COMPOSITION:

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

Excipients: maize starch, lactose, povidone, magnesium stearate, sodium starch glycollate, purified water.

PHARMACOLOGICAL CLASSIFICATION:

A 21.12 Hormone inhibitors

PHARMACOLOGICAL ACTION:

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

Tamoxifen also has weak oestrogenic effects.

After oral administration tamoxifen is readily absorbed with peak concentrations within 4 to 7 hours.

Steady state concentration (about 300 ng/ml) can be achieved after 4 weeks of treatment with 40 mg daily.

Tamoxifen is highly bound to serum proteins (>98 %).

Tamoxifen is metabolised predominantly to N-desmethyltamoxifen and to the minor metabolites, e.g. 4-hydroxytamoxifen.

Tamoxifen has a half-life of 7 days, while the half-life of N-desmethyltamoxifen is 14 days.

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

INDICATIONS:

Therapy for advanced disease:

KESSAR is indicated for the palliative treatment of certain types of advanced breast tumours.

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.

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. KESSAR is effective in delaying recurrence following total mastectomy and axillary dissection in postmenopausal women with breast cancer. In some adjuvant studies most of the benefit to date has been in the subgroup with 4 or more positive axillary nodes. The oestrogen and progesterone receptor values may help to predict whether adjuvant KESSAR therapy is likely to be beneficial.

CONTRA-INDICATIONS:

KESSAR is contra-indicated in patients with known hypersensitivity to tamoxifen or other ingredient of KESSAR.

KESSAR must not be given during pregnancy or to breast feeding women, and should be used with caution in women with functioning ovaries. (See PREGNANCY AND LACTATION).

WARNINGS:

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 oestrogen-

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. All patients should be advised to contact their doctors immediately, if they become aware of any symptoms of venous thromboembolism.

KESSAR tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

INTERACTIONS:

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

Medicines that are known to 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.

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 metabolites.

Various degrees of oestrogen effects on Papanicolau 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.

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

Co-administration with cytotoxic agents increases the risk for thromboembolic events.

Concomitant use of mitomycin (even in small doses) and KESSAR increases risk for haemolytic-uremic 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 of CYP3A4 enzymes.

Pharmacokinetic interaction with CYP2D6 inhibitors, showing a reduction in plasma level of an active tamoxifen metabolite, endoxifen, has been reported in the literature. The relevance of this to clinical practice is not known.

PREGNANCY AND LACTATION:

KESSAR is contra-indicated in pregnancy and lactation. (See CONTRA-INDICATIONS).

Tamoxifen was genotoxic in some *in-vitro* and *in-vivo* genotoxicity tests in rodents. Although adequate and well-controlled studies have not been done in humans, foetal deaths, spontaneous abortions and birth defects have been reported in patients receiving KESSAR.

Women of child-bearing 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 at least two months after discontinuation of KESSAR treatment.

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

It is not known whether tamoxifen is excreted in human milk. Because of the potential hazard to nursing infants, breast-feeding is not recommended during KESSAR treatment. (See CONTRA-INDICATIONS).

DOSAGE AND DIRECTIONS FOR USE:

The recommended daily dose is normally 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.

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 past 5 years.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

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

Side-effects:

Vascular disorder:

Frequent: Hot flushes

Frequency unknown: Thromboembolic events. There is an increased tendency to thrombophlebitis and thromboembolism. There is evidence of an increased incidence of cerebrovascular accidents and thromboembolic events, including deep vein thrombosis and pulmonary embolism, during KESSAR therapy. (See WARNINGS and INTERACTIONS).

Gastrointestinal disorders:

Frequent: Nausea and vomiting

Frequency unknown: Diarrhoea, abdominal cramps, constipation

Skin and subcutaneous tissue disorders:

Frequent: Rash, dry skin

Frequency unknown: Alopecia

Reproductive system and breast disorders:

Frequent: Menstrual irregularities (including amenorrhoea), pruritus vulvae, vaginal bleeding or discharge, endometrial carcinoma

Less frequent: Uterine sarcomas

Frequency unknown: Hyperplasia, polyps, uterine fibroids, reversible cystic ovarian swelling

Neoplasms benign and malignant (including cysts and polyps):

Frequency unknown: Hepatocellular cancer

Blood and lymphatic system disorders:

Less Frequent : Haemorrhagic episodes

Frequency unknown: Leucopenia, thrombocytopenia

Immune system disorders:

Frequency unknown: Hypersensitivity reaction (including urticaria, angioedema and dyspnoea)

Metabolism and nutrition disorders:

Frequency unknown: Fluid retention

Psychiatric disorders:

Frequency unknown: Depression, confusion

Nervous system disorders:

Frequency unknown: Headache, dizziness, light-headedness

Eye disorders:

Frequency unknown: Retinopathy, cataract, corneal changes, blurred vision, reduced visual acuity

Hepato-biliary disorders:

Less frequent: Severe hepatic abnormalities (including hepatic necrosis, hepatic failure)

Frequency unknown: Alterations of liver function parameters

Musculoskeletal, connective tissue and bone disorders:

Frequency unknown: Musculoskeletal pain, leg cramps

Other:

Frequency unknown: oedema, weight gain, pulmonary embolism, serum lipid changes, fatigue, cough, anorexia, hypertriglyceridaemia

Patients with bone metastases can experience a transient, sometimes severe increase in bone or tumour pain, often combined with hypercalcaemia, which may occur shortly after starting therapy. Local disease flare may also occur but generally subsides rapidly. These events may require temporary interruption of KESSAR treatment, with subsequent resumption of therapy at a reduced dosage, with gradual increase to the full dose.

Special Precautions:

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 withdrawn.

Premenopausal patients: Must be examined before treatment to exclude the possibility of pregnancy. Moreover, KESSAR may occasionally increase oestradiol plasma concentrations and may induce ovulation, exposing patients at risk of pregnancy. In pre-menopausal woman, KESSAR completely suppresses menstruation and cystic ovarian swelling may develop. Gonadal tumours in mice and liver tumours in rats receiving tamoxifen have been reported in long term studies. The clinical relevance of these findings has not been established.

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

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. Most ocular adverse reactions are reversible after KESSAR discontinuation.

Hepatocarcinogenicity of KESSAR has been reported in long-term carcinogenicity studies with rodents. Cases of hepatocellular carcinoma have also been reported in clinical KESSAR 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. It is recommended that the use of KESSAR as adjuvant therapy be limited to the maximum of 5 years for women with node-negative, oestrogen receptor-positive breast cancers who have had lumpectomy or mastectomy and radiation treatment.

Lactose intolerance: KESSAR tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Effects on ability to drive and use machines

The effect of KESSAR on the ability to drive or use machinery has not been systematically evaluated.

Since visual disturbances have been observed with the use of KESSAR, caution is advised when driving or using machines.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

On theoretical grounds, overdosage would be expected to cause enhancement of anti-oestrogenic 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.

IDENTIFICATION:

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

PRESENTATION:

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

STORAGE INSTRUCTIONS:

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

Keep out of reach of children.

REGISTRATION NUMBERS:

KESSAR 20 tablets: S/21.12/359

NAME AND BUSINESS ADDRESS OF APPLICANT:

Pfizer Laboratories (Pty) Ltd.

85 Bute Lane

Sandton, 2196

South Africa

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