1.3.1.1 Approved Professional Information for Medicines for Human Use

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

FENDEXAM FILM-COATED TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FENDEXAM FILM-COATED TABLETS:

Each film-coated tablet contains 30,4 mg of tamoxifen citrate, equivalent to 20 mg of tamoxifen.

Contains sugar: lactose monohydrate 227,78 mg.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off white, round, biconvex, unscored film-coated tablets debossed with ‘T20’ on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

FENDEXAM is indicated for the treatment of breast cancer. The response rate is similar to that seen with either oestrogens or androgens.

4.2. Posology and method of administration

Posology

Adults (including elderly):

The dose range is 20 mg to 40 mg daily given either in divided doses twice daily or as a single dose once daily.

Paediatric population:

The use of FENDEXAM is not recommended in children, as safety and efficacy have not been established (see section 5.1).

Method of administration

FENDEXAM film-coated tablets are taken orally.

4.3. Contraindications

- A known hypersensitivity to the active substance, tamoxifen, or to any of the excipients (see section 6.1)
- FENDEXAM 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).
- FENDEXAM is contraindicated in women who require concomitant coumarin-type anticoagulant therapy or in women with a history of deep-vein thrombosis or pulmonary embolus.

4.4. Special warnings and precautions for use

Rare cases of pancreatitis have been observed in association with FENDEXAM therapy, mostly in patients with pre-treatment elevated triglycerides. Very rarely, cases of interstitial pneumonitis have been reported.

Endometrial changes:

An increased incidence of endometrial cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours) has been reported in association with tamoxifen as in FENDEXAM treatment. The underlying mechanism is unknown but may be related to the oestrogen-like effect of tamoxifen as in FENDEXAM.

An increased incidence of endometrial changes including hyperplasia and polyps has been reported in association with tamoxifen as in FENDEXAM treatment. The incidence and pattern of this increase suggest that the underlying mechanism is related to the estrogenic properties of tamoxifen as in FENDEXAM.

There have been a few reports of endometriosis and uterine fibroids in women receiving tamoxifen as in FENDEXAM. The underlying mechanism may be due to the partial estrogenic effect of tamoxifen as in FENDEXAM. Ovarian cysts have also been observed in a small number of premenopausal patients with advanced breast cancer who have been treated with tamoxifen as in FENDEXAM.

Tamoxifen as in FENDEXAM has been reported to cause menstrual irregularity or amenorrhea.

Any women receiving or having previously received tamoxifen as in FENDEXAM, who report abnormal gynaecological symptoms, especially vaginal bleeding, should be promptly investigated.

Second tumours:

A number of second primary tumours, occurring at sites other than the endometrium and the opposite breast, have been reported in clinical trials. In animal studies high

doses of tamoxifen increases ALA synthase activity, although in man no reports of porphyric attacks have been associated with tamoxifen.

In an uncontrolled trial in 28 girls aged 2-10 years with McCune Albright Syndrome (MAS), who received 20 mg once a day for up to 12 months duration, mean uterine volume increased after 6 months of treatment and doubled at the end of the one-year study. While this finding is in line with the pharmacodynamic properties of tamoxifen, a causal relationship has not been established (see section 5.1).

Effects in Metastatic Breast Cancer Patients:

Hypercalcemia has been reported in some breast cancer patients with bone metastases within a few weeks of starting treatment with tamoxifen. If hypercalcemia does occur, appropriate measures should be taken and, if severe, FENDEXAM should be discontinued.

Thromboembolic effects:

There is evidence of an increased incidence of thromboembolic events, including deep-vein thrombosis and pulmonary embolism, during tamoxifen as in FENDEXAM therapy. When FENDEXAM is co-administered with chemotherapy, there may be a further increase in the incidence of thromboembolic effects. For treatment of breast cancer, the risks and benefits of FENDEXAM should be carefully considered in women with a history of thromboembolic events. In a small substudy (N = 81) of the NSABP-1 trial, there appeared to be no benefit to screening women for Factor V Leiden and Prothrombin mutations G20210A as a means to identify those who may not be appropriate candidates for tamoxifen therapy.

Effects on the Liver:

Tamoxifen as in FENDEXAM has been associated with changes in liver enzyme levels, and on rare occasions, a spectrum of more severe liver abnormalities including fatty liver, cholestasis, hepatitis and hepatic necrosis. A few of these serious cases included

fatalities. In most reported cases the relationship to tamoxifen is uncertain. However, some positive rechallenges and dechallenges have been reported.

Effects on the Eye:

Ocular disturbances, including corneal changes, decrement in colour vision perception, retinal vein thrombosis, and retinopathy have been reported in patients receiving tamoxifen as in FENDEXAM. An increased incidence of cataracts and the need for cataract surgery have been reported in patients receiving tamoxifen as in FENDEXAM.

General:

Decreases in platelet counts have been occasionally reported in patients taking tamoxifen as in FENDEXAM for breast cancer. In patients with significant thrombocytopenia, hemorrhagic episodes have occurred, but it is uncertain if these episodes are due to FENDEXAM therapy. Leukopenia has been observed, sometimes in association with anaemia and/or thrombocytopenia. There have been rare reports of neutropenia and pancytopenia in patients receiving tamoxifen FENDEXAM; this can sometimes be severe.

FENDEXAM contains lactose:

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

4.5. Interaction with other medicines and other forms of interaction

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

When FENDEXAM is used in combination with cytotoxic medicines, there is increased risk of thromboembolic events occurring (see sections 4.4 and 4.8).

The use of tamoxifen in combination with an aromatase inhibitor as adjuvant therapy has not shown improved efficacy compared with tamoxifen alone.
The known principal pathway for tamoxifen metabolism in humans is demethylation, catalysed by CYP3A4 enzymes. Pharmacokinetic interaction with the CYP3A4 inducing medicines rifampicin: showing a reduction in tamoxifen plasma levels have been reported in the literature. The relevance of this to clinical practice is not known.

Tamoxifen reduced letrozole plasma concentrations by 37 %. The effect of tamoxifen on metabolism and excretion of other antineoplastic medicines, such as cyclophosphamide and other medicines that require mixed function oxidases for activation, is not known.

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

Reduced efficacy of FENDEXAM has been reported with concomitant usage of some SSRI antidepressants (e.g., paroxetine) in some studies.

Co-administration of FENDEXAM with potent CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should whenever possible be avoided (see sections 4.4 and 5.2).
Pharmacokinetic interaction with CYP2D6 inhibitors, showing a reduction in plasma level of an active tamoxifen metabolite, 4-hydroxy-N-desmethyltamoxifen (endoxifen),

has been reported in the literature. The relevance of this in clinical practice is not known.

Rifampicin can induce the metabolism and reduce the plasma concentration of tamoxifen, as in FENDEXAM.

Aminoglutethimide reduces FENDEXAM and N-desmethyl tamoxifen plasma concentrations.

Medroxyprogesterone reduces plasma concentrations of N-desmethyl, but not tamoxifen.

Concomitant use of mitomycin (even in small doses) and FENDEXAM increases the risk for haemolyticuraemic syndrome, anaemia and thrombocytopenia. Concomitant use should be avoided.

Concomitant bromocriptine therapy has been shown to elevate serum FENDEXAM and N-desmethyl tamoxifen.

Based on clinical and pharmacokinetic results from the anastrozole adjuvant trial, FENDEXAM should not be administered with anastrozole.

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 FENDEXAM.

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

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

4.6. Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and female

Women should be advised not to become pregnant whilst taking FENDEXAM and should use barrier or other non-hormonal contraceptive methods if sexually active. Pre-menopausal women must be carefully examined before treatment to exclude pregnancy. Women should be informed of the potential risks to the foetus, should they become pregnant whilst taking FENDEXAM or within 2 months of cessation of therapy.

Pregnancy

FENDEXAM must not be administered during pregnancy. There have been reports of spontaneous abortions, birth defects and foetal deaths after women have taken FENDEXAM.

In rodent models of foetal reproductive tract development, FENDEXAM was associated with changes similar to those caused by oestradiol, ethynyloestradiol, clomiphene and diethylstilboestrol (DES). Although the clinical relevance of these changes is unknown, some of them, especially vaginal adenosis, are similar to those seen in young women who were exposed to DES in utero and who have a 1 in 1 000 risk of developing clear-cell carcinoma of the vagina or cervix.

Breastfeeding

It is not known if FENDEXAM is excreted in human milk and therefore the medicine is not recommended during breastfeeding.

Fertility

FENDEXAM does not cause infertility, even in the presence of menstrual irregularity.

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

When adverse effects are severe, it may be possible to control them by a simple reduction of dosage (within the recommended dosage range) without loss of control of the disease. If adverse effects do not respond to this measure, it may be necessary to stop the treatment.

Tamoxifen was not mutagenic in a range of *in vitro* and *in vivo* mutagenicity tests.

Tamoxifen was genotoxic in some *in vitro* tests and *in vivo* genotoxicity tests in rodents.

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.

a. *Summary of the safety profile*

The most frequent adverse effects for FENDEXAM are hot flushes and menstruation suppression.

b. *Tabulated list of adverse reactions*

System Organ Class	Frequency	Adverse event
Neoplasms benign, malignant and unspecified(including cysts and polyps)	Frequent	Uterine fibroids, endometrial cancer
	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	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	Frequent	Thromboembolic events (including deep vein thrombosis, microvascular thrombosis and pulmonary embolism), hot flushes
	Unknown	Thrombophlebitis and thromboembolism
Respiratory, thoracic and mediastinal disorders	Less frequent	Interstitial pneumonitis
	Unknown	Cough

Gastrointestinal disorders	Frequent	Nausea, 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		
	Frequent	Skin rash, 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	Frequent	Pruritus vulvae, endometrial changes (including hyperplasia and polyps), menstrual irregularities (including amenorrhoea) in pre-menopausal patients, vaginal bleeding, vaginal discharge
	Less frequent	Endometriosis, cystic ovarian swelling, vaginal polyps
Congenital, familial and genetic disorders	Less frequent	Porphyria cutanea tarda
General disorders and administration site conditions	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

c. Description of selected adverse reactions

Metastatic Breast Cancer:

Increased bone and tumour pain and, also, local disease flare have occurred, which are sometimes associated with a good tumour response. Patients with increased bone pain may require additional analgesics. Patients with soft tissue disease may have sudden increases in the size of pre-existing lesions, sometimes associated with marked erythema within and surrounding the lesions and/or the development of new lesions. When they occur, the bone pain or disease flare are seen shortly after starting FENDEXAM and generally subside rapidly.

d. Other special population

Male Breast Cancer:

FENDEXAM is well tolerated in males with breast cancer. Reports from the literature and case reports suggest that the safety profile of tamoxifen in males is similar to that seen in women. Loss of libido and impotence have resulted in discontinuation of FENDEXAM therapy in male patients. Also, in oligospermic males treated with FENDEXAM, LH, FSH, testosterone and oestrogen levels were elevated. No significant clinical changes were reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the ‘6.04 Adverse Drug Reactions Reporting Form’. Found 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 the pharmacological side effects. Animal studies showed that extreme overdosage (100 - 200 times the recommended daily dose) may produce oestrogenic effects.

There have been reports in the literature that tamoxifen given at several time 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and class: A 21.12 Hormone inhibitors

Pharmacotherapeutic group: Anti-oestrogens, ATC code: L02BA01

Mechanism of action

Tamoxifen is a non-steroidal, triphenylethylene-based medicine which displays a complex spectrum of oestrogen antagonist and oestrogen-like pharmacological effects in different tissues. In breast cancer patients, at the tumour level, tamoxifen acts primarily as an antioestrogen, preventing oestrogen binding to the oestrogen receptor.

In the clinical situation, it is recognised that tamoxifen leads to reductions in levels of blood total cholesterol and low density lipoproteins in postmenopausal women.

An uncontrolled trial was undertaken in a heterogeneous group of 28 girls aged 2 to 10 years with McCune Albright Syndrome (MAS), who received a 20 mg dose once a day for up to 12 months duration. Among the patients who reported vaginal bleeding during the pre-study period, 62 % (13 out of 21 patients) reported no bleeding for a 6-month period and 33 % (7 out of 21) reported no vaginal bleeding for the duration of the trial.

Mean uterine volume increased after 6 months of treatment and doubled at the end of

the 1 year study. While this finding is in line with the pharmacodynamic properties of tamoxifen, a causal relationship has not been established. There are no long-term safety data in children. In particular, the long term effects of tamoxifen on growth, puberty, and general development have not been studied.

5.2. Pharmacokinetic properties

Absorption

After oral administration, tamoxifen is rapidly absorbed with maximum serum concentrations attained within 4 - 7 hours. Steady state concentrations (about 300 ng/ml) are achieved after 4 weeks' treatment with 40 mg daily.

Distribution

The medicine is highly protein bound to serum albumin (> 99 %).

Biotransformation

Tamoxifen is extensively metabolized after oral administration. Metabolism is by hydroxylation, demethylation and conjugation. N-desmethyl tamoxifen is the major metabolite found in patients' plasma. The biological activity of N-desmethyl tamoxifen appears to be similar to that of tamoxifen. 4-Hydroxytamoxifen and a side chain primary alcohol derivative of tamoxifen have been identified as minor metabolites in plasma. Tamoxifen is a substrate of cytochrome P-450 3A, 2C9 and 2D6, and an inhibitor of P-glycoprotein.

Elimination

Excretion occurs primarily via the faeces. An elimination half-life of approximately 7 days has been calculated for the medicine itself, whereas that for N-desmethyltamoxifen is 14 days.

In a clinical study where girls between 2 and 10 years with McCune Albright Syndrome (MAS) received 20 mg tamoxifen once a day for up to 12 months duration, there was an age-dependent decrease in clearance and an increase in exposure (AUG), (with values up to 50 % higher in the youngest patients) compared with adults.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

FENDEXAM film-coated tablets contain the following inactive ingredients:

Lactose Monohydrate, corn starch, povidone K 30, croscarmellose sodium, magnesium stearate, purified water.

Film-coating composition : Opadry white 02B58900 (hypromellose, titanium dioxide, macrogol/PEG), purified water.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 °C.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

FENDEXAM film-coated tablets are packed in white opaque round 60 ml HDPE container closed with white opaque polypropylene child resistant 33 mm closure with wad having induction sealing liner, in a pre-printed carton with package leaflet.

Pack size: 30s

6.6. Special precautions for disposal and other handling

No special requirements.

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

AUROGEN SA (Pty) Ltd

Woodhill Office Park, Building 1, First Floor

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

8. REGISTRATION NUMBER

56/21.12/0699.698

9. DATE OF FIRST AUTHORISATION

09 MAY 2023