TREMOFID 30T PI1541

TREMOFID ID PI001001

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TREMOFID film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TREMOFID 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

TREMOFID 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 **TREMOFID** is not recommended in children, as safety and efficacy have not been established (see section 5.1).

Method of administration

TREMOFID 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).
- **TREMOFID** 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).
- **TREMOFID** 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 **TREMOFID** 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 **TREMOFID**. Treatment. The underlying mechanism is unknown but may be related to the oestrogen-like effect of tamoxifen, as in **TREMOFID**.

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

There have been a few reports of endometriosis and uterine fibroids in women receiving tamoxifen, as in **TREMOFID**. The underlying mechanism may be due to the partial estrogenic effect of tamoxifen, as in **TREMOFID**. 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 **TREMOFID**.

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

Any women receiving or having previously received tamoxifen, as in **TREMOFID**, 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 5-aminolevulinic acid (ALA) synthase activity, although in man no reports of porphyric attacks have been associated with use of 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, **TREMOFID** 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 **TREMOFID** therapy. When **TREMOFID** 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 **TREMOFID** should be carefully considered in women with a history of thromboembolic events. In a small substudy (N = 61) 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 **TREMOFID** 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 **TREMOFID**. An increased incidence of cataracts and the need for cataract surgery have been reported in patients receiving tamoxifen, as in **TREMOFID**.

General:

Decreases in platelet counts have been occasionally reported in patients taking tamoxifen, as in **TREMOFID** for breast cancer. In patients with significant thrombocytopenia, haemorrhagic episodes have occurred, but it is uncertain if these episodes are due to **TREMOFID** 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 **TREMOFID**, this can sometimes be severe.

TREMOFID *contains lactose:*

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

4.5. Interaction with other medicines and other forms of interaction

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

When **TREMOFID** 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 the use of 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 aminoheptanic 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 **TREMOFID** in order to avoid bleeding during the possible thrombocytopenic period.

Reduced efficacy of **TREMOFID** has been reported with concomitant usage of some Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants (e.g., paroxetine) in some studies.

Co-administration of **TREMOFID** with potent CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should wherever 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 **TREMOFID**.

Aminoglutathimide reduces **TREMOFID** 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 **TREMOFID** increases the risk for haemolytic/uraemic syndrome, anaemia and thrombocytopenia. Concomitant use should be avoided.

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

Based on clinical and pharmacokinetic results from the anastrozole adjuvant trial, **TREMOFID** 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 **TREMOFID**.

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

Increased serum thyroxine levels, likely due to an increase in thyroxine-binding globulin, may occur in patients who are receiving **TREMOFID**, 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 **TREMOFID** 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 **TREMOFID** or within 2 months of cessation of therapy.

Pregnancy

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

In rodent models of foetal reproductive tract development, **TREMOFID** was associated with changes similar to those caused by oestradiol, ethynyloestradiol, diorophene 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 **TREMOFID** is excreted in human milk and therefore **TREMOFID** is not recommended during breastfeeding.

Fertility

TREMOFID 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 **TREMOFID**; 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 **TREMOFID** 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

✂ DETACH BEFORE DISPENSING

SCHEDULING STATUS

S4

PATIENT INFORMATION LEAFLET

TREMOFID Film-coated tablets

Tamoxifen

Contains sugar: Lactose monohydrate 227,78 mg.

Read all of this leaflet carefully before you take TREMOFID

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist, nurse or other health care provider.
- **TREMOFID** has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet

1. What **TREMOFID** is and what it is used for
2. What you need to know before you take **TREMOFID**
3. How to take **TREMOFID**
4. Possible side effects
5. How to store **TREMOFID**
6. Contents of the pack and other information

1. What TREMOFID is and what it is used for

TREMOFID belongs to a group of medicines called anti-oestrogens and is used for the treatment of breast cancer.

2. What you need to know before you take TREMOFID

Do not take TREMOFID:

- If you are hypersensitive (allergic) to tamoxifen or any of the ingredients of **TREMOFID** (listed in section 6)
- If you are pregnant or if you are breastfeeding
- If you are taking any anticoagulants (blood thinning agents) such as warfarin
- If you are a women with a personal or family history of thromboembolism (blood clots),venous thromboembolism (or blood clots in the vein of the leg), stroke.

Warnings and precautions

Tell your doctor or healthcare professional before taking **TREMOFID**:

- If you have a history of stroke or blood clot;
- If you have liver disease;
- If you have high cholesterol or triglycerides (a type of fat in the blood)
- If you have a history of cataracts.
- If you have a history of deep vein thrombosis (blood clots in the veins of your legs), pulmonary embolism (blood clots in your lungs) or any clotting disorders. If you become aware of such events you should contact your doctor
- If you have low levels of white blood cells or platelets in your blood. This can make you bruise more easily, get serious infections, or feel very tired or breathless
- If you have high levels of calcium in your blood. Signs of this include feeling very thirsty, feeling sick (nausea) and vomiting.

Tell your doctor immediately if you notice any of the following once you start treatment with **TREMOFID**:

- Vaginal bleeding
- New breast lumps
- Pelvic pain or pressure
- Changes in your vision

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before being given **TREMOFID**.

Children and adolescents

TREMOFID has not been studied in children or adolescents and therefore should not be used in this patient population.

Other medicine and TREMOFID:

Always tell your healthcare professional if you are taking any other medicine (this includes complementary or traditional medicines).

The use of **TREMOFID** with these medicines may cause undesirable interactions.

In particular tell your doctor if you are using the following medicines:

- To thin your blood – eg. Warfarin
- Chemotherapy
- Letrozole (used for breast cancer)
- Anastrozole(used for breast cancer)
- Bromocriptine (used for pituitary tumours, increased prolactin in the blood)
- Rifampicin
- Medroxyprogesterone (contraceptive medicine)
- Aminoglutathimide

Pregnancy, breastfeeding and fertility

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other healthcare provider for advice before **TREMOFID**.

You should not get pregnant while taking **TREMOFID** or for two months after stopping treatment with **TREMOFID**. Use a barrier contraceptive method or non-hormonal contraception (eg. condoms, diaphragm, spermicides, intrauterine devices), to prevent pregnancy.

TREMOFID may harm your unborn baby if you are pregnant.

Do not breastfeed your baby while taking **TREMOFID**. It may harm your baby.

Driving and using machines

It is not always possible to predict to what extent **TREMOFID** may interfere your daily activities. Do not engage in the above activities until you are aware of the measure to which **TREMOFID** affects you.

TREMOFID contains lactose

TREMOFID contains 227,78 mg of lactose monohydrate per film-coated tablet.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking **TREMOFID**.

3. How to take TREMOFID

Do not share medicines prescribed for you with any other person. Always take **TREMOFID** exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

The usual dose is one to two tablets, taken once a day or in divided doses taken twice a day.

Your doctor will tell you how long your treatment with **TREMOFID** will last. Do not stop any treatment unless your doctor tells you to do so. If you have the impression that the effect of **TREMOFID** is too strong or too weak, tell your doctor or pharmacist.

If you take more TREMOFID than you should

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison centre.

If you forget to take TREMOFID

Do not take a double dose to make up for forgotten individual doses.

4. Possible side effects

TREMOFID can have side effects.

Not all side effects reported for **TREMOFID** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking **TREMOFID**, please consult your doctor, pharmacist or other healthcare professional for advice.

If any of the following happens, stop taking **TREMOFID** and tell your doctor immediately or go to the casualty department at your nearest hospital:

- Pain and/or swelling in the legs
- Sudden chest pain, shortness of breath and/or coughing up blood
- Difficulty walking or talking, numbness and/or weakness
- Vaginal bleeding, period irregularities, unusual vaginal discharge, pain or pressure in lower pelvis.

These are all very serious side effects which may indicate a stroke.

- blood clot or changes to your uterus (womb). If you have them, you may have had a serious reaction to **TREMOFID**. You may need urgent medical attention or hospitalisation.

Treatment with **TREMOFID** can very commonly cause hot flushes and changes in your period (menstruation).

Tell your doctor if you notice any of the following:

Frequent side effects:

- Non-cancerous growths in the womb, cancer of the lining of the womb. this may cause pain or pressure in the pelvis (lower tummy) or irregular vaginal bleeding
- Weight gain
- Headaches
- Dizziness
- Hot flushes
- Coughing
- Nausea
- Stomach pain
- Leg cramps
- Bone pain
- Period irregularities
- Vaginal bleeding/discharge
- Itching of the genital area
- Water retention
- Weakness
- Hair loss
- Stroke/DVT (deep vein thrombosis)
- Anaemia (a blood condition which means you have too few red blood cells)
- Itching of genitals

Less frequent side effects:

- Increase in blood calcium levels (hypercalcaemia). This may cause loss of appetite, nausea and vomiting, tiredness, weakness and muscle pain
- Dry cough and shortness of breath (interstitial pneumonitis)
- Pancreatitis (pain or tenderness in your upper abdomen), mostly in patients with increased levels of fat in the blood before treatment with **TREMOFID**
- Swelling of the face, lips, tongue or throat, difficulty in swallowing or breathing (angioedema).
- Stevens -Johnson syndrome (a rare, serious disorder of the skin and mucous membranes, usually a reaction to medication)
- Inflammation of small blood vessels in the skin leading to skin rash (cutaneous vasculitis)
- Bullous pemphigoid (large, fluid-filled blisters).
- Erythema multiforme (bull's-eye-shaped lesions).
- Inflammation of the skin characterised by rash or erythema, very often on areas exposed to light (a condition called cutaneous lupus erythematosus)
- Presence of tissue similar to the lining of the uterus at other sites in the pelvis (endometriosis).
- Sharp dull pain in the lower abdomen accompanied by bloating and swelling. This may be due to swelling of the ovarian cyst
- Non-cancerous mass in the inner lining of the vagina (called vaginal polyp)
- Blisters on skin that's exposed to the sun, including the hands, face, and arms(Porphyria cutanea tarda)
- Radiation recall - a tissue reaction that develops on skin that previously received radiation therapy
- Cataracts
- Stroke
- Blood clots
- Lung disease
- Cancers of the uterus (womb)
- Liver problems
- Increase fat in the blood
- Lack of white blood cells (neutropenia)

Frequency unknown

- Liver cancer
- Loss of appetite,
- Depression, confusion
- Cerebrovascular accidents (a loss of blood flow to part of the brain, which damages brain tissue)
- Dizziness
- Inflammation of the vein, cough
- Swelling due to retained fluid
- Severe increase in bone and tumour pain
- Weight gain
- Stomach aches

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects via https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of **TREMOFID**

5. How to store TREMOFID

STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

Store at or below 25 °C.

- Keep the container in the outer carton in order to protect from light.
- Do not use after the expiry date stated on the container and the carton.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of the pack and other information

What TREMOFID contains

The active substance is tamoxifen.

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

Contains sugar: lactose monohydrate 227,78 mg.

The other ingredients of **TREMOFID** are:

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

Film-coating composition : Opadry white 02B59900 (hypromellose, titanium dioxide, macrogol/PEG), purified water.

What TREMOFID looks like and contents of the pack

TREMOFID is a white to off white, round, biconvex, unscored film-coated tablets debossed with 'T20' on one side and plain on the other side.

TREMOFID 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

NAME, BUSINESS ADDRESS AND TELEPHONE NUMBER OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

AUROGEN SA (PTY) LTD
Woodhill Office Park, Building 1, First Floor
53 Phillip Engelbrecht Avenue
Meyerspal, Ext. 12, 1448
Johannesburg
South Africa

This leaflet was last revised in

29 September 2023

REGISTRATION NUMBER

56/21.12/0588

System Organ Class	Frequency	Adverse event
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, lightheadedness, 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 tumorgi 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 **TREMOFID** and generally subside rapidly.

d. Other special population

Male Breast Cancer:

TREMOFID 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 **TREMOFID** therapy in male patients. Also, in oligospermic males treated with **TREMOFID**, luteinizing hormone (LH), follicle-stimulating hormone (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 (AUC), (with values up to 50 % higher in the youngest patients) compared with adults.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

TREMOFID 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 02B59900 (hypromellose, titanium dioxide, macrogol/PEG), purified water.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store at or below 25 °C.

Keep HDPE container tightly closed.

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

TREMOFID film-coated tablets are packed in white opaque round 60 ml HDPE container closed with white opaque polypropylene child resistant 33 mm closure with seal 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
Meyerdal, Ext. 12, 1448
Johannesburg
South Africa

8. REGISTRATION NUMBER

56/21.12/0588

9. DATE OF FIRST AUTHORISATION

29 SEPTEMBER 2023

P154/1291

✂ DETACH BEFORE DISPENSING

SKEDULERINGSTATUS

S4

PASIËNTINLIGTINGSBLAD
TREMOFID Filmbedekte tablette
Tamoksifeen
Bevat sukker: Laktosemonohidraat 227,78 mg.

Lees hierdie inligtingsblad noukeurig deur voordat jy TREMOFID neem

- Hou hierdie inligtingsblad. Dit mag nodig wees om dit later weer te lees.
- Indien jy enige vrae/ons vrae het, vra gerus jou dokter, apteker, verpleegkundige of ander gesondheidsorgverskaffer.
- **TREMOFID** is vir jou persoonlik voorgeskryf en jy moenie jou medisyne met ander persone deel nie. Dit kan skadelik wees vir hulle, al is hulle simptome dieselfde as joune.

Wat is in hierdie inligtingsblad:

1. Wat is **TREMOFID** en waarvoor word dit gebruik
2. Wat jy moet weet voordat jy **TREMOFID** neem
3. Hoe om **TREMOFID** te neem
4. Moontlike nawe-effekte
5. Hoe om **TREMOFID** te bewaar
6. Inhoud van die verpakking en ander inligting

1. Wat is TREMOFID en waarvoor word dit gebruik

TREMOFID behoort aan 'n groep mediisynes genaamd anti-estrogene en word vir die behandeling van borskanker gebruik.

2. Wat jy moet weet voordat jy TREMOFID neem

Moenie TREMOFID neem nie:

- Indien jy hipersensitief (allergies) vir tamoksifeen of vir enige van die bestanddele van **TREMOFID** is (gelys by afdeling 6).
- Indien jy swanger is of borsvoed.
- Indien jy enige antikoagulante (bloedverdunners), soos warfarien, neem.
- Indien jy 'n vrou met 'n persoonlike of familiegeskiedenis van trombo-embolisme (bloedklonte), veneuse trombo-embolisme (bloedklonte in die are van die been) of beroerte is.

Waarskuwings en voorsorgmaatreëls

Sê vir jou dokter of gesondheidsorgbeskikundige voordat jy **TREMOFID** neem:

- Indien jy 'n geskiedenis van beroerte of bloedklonte het;
- Indien jy aan leweraalse ly;
- Indien jy hoë cholesterol of triglyseriede het ('n soort vet wat in jou bloed voorkom);
- Indien jy 'n geskiedenis van kataraktes het.
- Indien jy 'n geskiedenis van diepveentrombose (bloedklonte in die are van jou bene), pulmonale embolisme (bloedklonte in jou longe) of enige stollingsversteurings het. Indien jy bevrees raak van suike gebeure, kontak jou dokter.
- Indien jy nie vlekke van witbloedselle of plaatjies in jou bloed het. Dit kan veroorsaak dat jy makliker kneus, ernstige infeksies kry, of baie moeg en uitasem voel.
- Indien jy hoë kalsiumvlakke in jou bloed het. Tekens hiervan sluit in erge dors, naarheid (voel mislik) en braking.

Sê onmiddellik vir jou dokter indien jy enige van die volgende opmerk nadat jou behandeling met **TREMOFID** begin het:

- Vaginale bloeding
- Nuwe knoppe in die bors
- Pyn of gevoel van druktking in die bekken (onderstedeel van die buik)
- Veranderings in jou vleis.

Indien jy omseker is of enige van bogenoemde op jou van toepassing is, bespreek dit met jou dokter of apteker voordat jy hierdie mediisyne ontvang.

Kinders en adolessente

TREMOFID is nie by kinders of adolessente bestudeer nie en behoort gevolglik nie in hierdie pasiëntpopulasie gebruik te word nie.

Ander mediisynes en TREMOFID:

Sê altyd vir jou gesondheidsorgbeskikundige indien jy enige ander mediisyne neem (dit sluit komplementêre of tradisionele mediisynes in). Gebruik van **TREMOFID** saam met hierdie mediisynes kan ongewenste interaksies veroorsaak.

Sê veral vir jou dokter indien jy enige van die volgende mediisynes gebruik:

- Om jou bloed te verdun – bv. warfarien;
- Chemoterapie;
- Letrozool (gebruik vir borskanker);
- Anastrozool (gebruik vir borskanker);
- Broomkriptien (gebruik vir pituïtêre gewasse, verhoogde prolaktienvlak in die bloed);
- Rifampisien;
- Medroksiprogesteron (kontraseptiewe mediisyne);
- Aminoglutetimied.

Swangerskap, borsvoeding en vrugbaarheid

Indien jy swanger is of jou baba bonsoved, vermoed dat jy swanger mag wees of beplan om swanger te raak, raadpleeg asseblief jou dokter, apteker of ander gesondheidsorgbeskuffer voordat jy **TREMOFID** neem.

Jy moenie swanger raak terwyl jy **TREMOFID** neem of vir twee maande nadat behandeling met **TREMOFID** gestaak is nie. Gebruik 'n aksaneerdede vorm van voorbehoeding of nie-hormonale kontraseptiewe (bv. kondisme, diafragma, spermdoders, intra-uteriene apparaat) om swangerskap te voorkom.

Indien jy swanger is, kan **TREMOFID** skadelik vir jou ongebore baba wees.

Moenie jou baba bonsoved terwyl jy **TREMOFID** neem nie. Dit kan skadelik wees vir jou baba.

Bestuur en gebruik van masjiene

Dit is nie altyd moontlik om te voorspel tot watter mate **TREMOFID** met jou daaglikse aktiwiteite mag inmeng nie. Verseker asseblief dat jy nie bogenoemde aktiwiteite uitvoer nie, totdat jy weet tot watter mate **TREMOFID** jou affekteer.

TREMOFID bevat laktose

TREMOFID bevat 227,78 mg laktoseamonohidraat per filmbedekte tablet.

Indien jou dokter jou ingelig het dat jy onverdraagsaam vir sekere suikers is, kontak jou dokter voordat jy **TREMOFID** neem.

3. Hoe om TREMOFID te neem

Moenie mediisynes wat vir jou voorgeskryf is, met enigemand anders deel nie. Neem **TREMOFID** altyd presies soos wat jou dokter vir jou aangedui het. Vra gerus jou dokter of apteker indien jy onseker is.

Die gebruiklike dosis is een tot twee tablette, een keer per dag geneem of twee keer per dag in verdeelde dosisse geneem.

Jou dokter sal jou mitg hoe lank jou behandeling met **TREMOFID** gaan duur. Moenie enige behandeling staak nie, behalwe as jou dokter sê jy moet.

Indien jy die indruk kry dat die uitwerking van **TREMOFID** te sterk of te swak is, bespreek dit met jou dokter of apteker.

Indien jy meer TREMOFID neem as wat jy moet

In geval van oordosering, raadpleeg jou dokter of apteker. Indien nie een van hulle beskikbaar is nie, kontak die naaste hospitaal of gifsentrum.

Indien jy vergeet om TREMOFID te neem

Moenie 'n dubbele dosis neem om te vergoed vir die individuele dosisse wat oorgeslaan is nie.

4. Moontlike nawe-effekte

TREMOFID kan nawe-effekte hê.

Nie alle nawe-effekte wat vir **TREMOFID** gerapporteer is, word in hierdie inligtingsblad ingelsit nie. Indien jou algemene gesondheid nou verswak of indien jy enige ongunstige effekte ondervind terwyl jy **TREMOFID** neem, moet jy asseblief jou dokter, apteker of ander gesondheidsorgbeskuldige raadpleeg.

Indien enige van die volgende voorkom, hou op om **TREMOFID** te neem en sê onmiddellik vir jou dokter of gaan na die ongevalsafdeling by jou naaste hospitaal:

- Pyn en/of swelling in die bene;
- Skielike pyn in die bors, kortasemheid en/of jy hoes bloed uit;
- Sukkel om te loop of te praat, gevoelloosheid en/of swakheid;
- Vaginale bloeding, ongewaarde menstruasie, ongewone vaginale afskeiding, pyn of druktking in onderste deel van bekken.

Hierdie is baie ernstige nawe-effekte wat 'n benarde, bloedklont of verandernings in jou uterus (baarmoeder) kan aandui. Indien jy enige daarvan ondervind, mag jy 'n ernstige reaksie op **TREMOFID** gehad het. Jy mag dringend mediese bystand of hospitaalsorge benodig.

Dit is baie algemeen dat behandeling met **TREMOFID** warm gloede en verandernge in jou maandsonde (menstruasie) veroorsaak.

Sê vir jou dokter indien jy enige van die volgende opmerk:

Nawe-effekte wat dikwels voorkom:

- Nie-kwaadaardige gewasse in die baarmoeder, kanker van die baarmoederslymvlies. Dit kan pyn of druktking in die bekken (onderste deel van die buik) of onreëlmatige vaginale bloeding veroorsaak.
- Gewigstoename
- Hoofpyne
- Duiseligheid
- Warm gloede
- Hoes
- Naarheid
- Maagpyn
- Krampe in die bene
- Pyn in skeletbene
- Ongereelde menstruasie
- Vaginale bloeding/afskeiding
- Gejeuk in die genitale area
- Waterterughouding
- Seerheid
- Hiservlerles
- Bereete/DVT (diepveentrombose)
- Anemie (n bloedtoestand wat beteken jy het te min rooibloedselle)
- Gejeuk van geslagsdele

Nawe-effekte wat minder dikwels voorkom:

- Styging in bloedkalsiumvlakke (hiperkalsemie). Dit kan aptytverlies, naarheid en braking, moegheid, swakheid en spierpyn veroorsaak
- Droë hoes en kortasemheid (interstisiële pneumonitis)
- Pankreatitis (pyn of heerhaid bo in jou buik), meeral by pasiënte wat voor behandeling met **TREMOFID** verhoogde vetvlakke in die bloed gehad het
- Swelling van die gesig, lippe, tong of keel, sukkel om te sluk of asem te haal (angio-edeem)
- Stevens-Johnson-sindroom ('n seldsame, ernstige versteuring van die vel en slymvlies, gewoonlik 'n reaksie op mediksaie)
- Inflammasie van klein bloedvate in die vel, wat lei tot 'n velurtalag (kutane vaskulitis)
- Bulleuse pemfigoïed (groot, voggevulde blase)
- Erythema multiforme (ringvormige letsels)
- Inflammasie van die vel gekenmerk deur uitslag of erteem, baie dikwels by dele wat aan lig blootgestel word ('n toestand wat kutane lupus erlematosus genoem word)
- Teenoorgidheid van weefsel soortgelyk aan die baarmoederslymvlies by ander plekke in die bekken (endometriose)
- Skerp, dowwe pyn in onderste deel van die buik, met gepaardgaande opgeblasenheid en swelling. Dit mag weens swelling van 'n ovariale sist wees
- Nie-kwaadaardige gewas in die binneste voering van die vagina (genoem vaginale polipe)
- Blase op vel wat aan die son blootgestel is, insluitende die hande, gesig en arms (porphyria cutanea tarda)
- Bestralingsherroeping – 'n seefsiekreaksie wat ontwikkel op vel wat voorheen bestralingsterapie ontvang het
- Kataraktes
- Bensorte
- Bloedklonte
- Longsiekte
- Kanker van die uterus (baarmoeder)
- Lewerprobleme
- Stygting van vette in die bloed
- Gebrek aan witbloedselle (neutropenie)

Nawe-effekte waarvan die frekwensie onbekend is:

- Lewerkanker
- Verlies aan eetlus
- Depressie, verwardheid
- Sensitiveiteitsverlies veroorsaak deur 'n tekort aan die bloedvloei na 'n deel van die brein, wat breinweefsel beskadig)
- Duiseligheid
- Asembenaling, hoes
- Swelling weens vog wat teruggehou word
- Hewige vereergering van bees- en tumorpyn
- Gewigstoename
- Maagpyn.

Indien jy enige nawe-effekte opmerk wat nie in hierdie inligtingsblad genoem word nie, lig asseblief jou dokter of apteker daarvoor in.

Rapportering van nawe-effekte

Indien jy nawe-effekte ondervind, bespreek dit met jou dokter, apteker of verpleegkundige. Dit sluit enige moontlike nawe-effekte wat nie in hierdie inligtingsblad gelys is nie. Jy kan ook nawe-effekte rapporteer via https://www.sahpra.org.za/Publications/Index/8. Deur nawe-effekte te rapporteer, kan jy help om meer inligting rakende die veiligheid van **TREMOFID** te verkry.

5. Hoe om TREMOFID te bewaar

BEWAAR ALLE MEDISYNES BUITE BEREIK VAN KINDERS.

Bêre by of onder 25 °C.
Hou die houer in die buitenste karton om lean lig te beskerm.
Moenie gebruik nà die vervaldatum wat op die bottel en die karton voorkom nie.

Neem alle ongebruikte mediisyne terug na jou apteker.
Moenie ongebruikte mediisyne in dreine en riooltelsels (bv. toilette) wegdoen nie.

6. Inhoud van die verpakking en ander inligting

Wat TREMOFID bevat

Die aktiewe bestanddeel is tamoksifeen.
Elke filmbedekte tablet bevat 30,4 mg tamoksifeensitraat, gelykstaande aan 20 mg tamoksifeen.
Bevat sukker: 227,78 mg laktoseamonohidraat.

Die ander bestanddele van **TREMOFID** is:
laktoseamonohidraat, mielisetylsel, povidoon K 30, natriumkruiskarmelkose, magnesiumstearaat, gesuiwerde water.
Samestelling van filmlagie: Opadry White 02B59900 (hipromelliose, titaandioksied, makrogol/PEG), gesuiwerde water.

Hoe TREMOFID lyk en inhoud van die verpakking

TREMOFID is 'n wit tot naaswit, ronde, bikonvekse, filmbedekte tablet met '720' aan die een kant ingepers en glad aan die ander kant, sonder 'n breeklyn.

TREMOFID filmbedekte tablette word verpak in 'n wit, ondeursigtige, ronde, 60 ml HDPE-houer met 'n wit, ondeursigtige, 33 mm kindbestande polipropileen-deksel met weëlepreg en 'n induksieseëlvoering, in 'n voorafbedrukte karton met 'n inligtingsblad.

Verpakkingsgrootte: 30's

NAAM, BESIGHEIDSADRES EN TELEFOONNOMMER VAN DIE HOUER VAN DIE REGISTRASIESERTIFIKAAT

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Hierdie inligtingsblad is laas hersien

29 September 2023

REGISTRASIENOMMER

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