PROFESSIONAL INFORMATION

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SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

TAMOPLEX (Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

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

Contains sugar: 99,35 mg lactose monohydrate.

For full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

TAMOPLEX: White biconvex tablets with a diameter of 9 mm, without inscription.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Therapy for advanced disease:

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

Adjuvant therapy:

TAMOPLEX 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 oestrogen receptor positive (HER2).

Data is insufficient to predict which women are most likely to benefit and to determine if TAMOPLEX provides any benefit in women with tumours of less than 1 cm. TAMOPLEX 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 TAMOPLEX therapy is likely to be beneficial.

4.2 Posology and method of administration:

Posology:

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.

A response is usually not achieved until after a treatment period of 2 to 3 months.

In the management of advanced disease, TAMOPLEX 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 suggests that no further therapeutic advantage is gained if the treatment is prolonged past 5 years.

Method of administration:

For oral administration.

4.3 Contraindications:

TAMOPLEX is contraindicated in:

- Hypersensitivity to any of the ingredients, including excipients.
- TAMOPLEX should not be given during pregnancy and should be used with caution in women with functioning ovaries.
- The safety of TAMOPLEX in lactation has not been established.

4.4 Special warnings and precautions for use:

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with TAMOPLEX treatment. At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, TAMOPLEX should be withdrawn immediately and an alternative treatment considered (as appropriate). If the patient has developed a serious reaction such as SJS or TEN with the use of TAMOPLEX, treatment with this medicinal product must not be restarted in this patient at any time.

In patients with hereditary angioedema, TAMOPLEX may induce or exacerbate symptoms of angioedema.

Suppression of menstruation:

Menstruation is suppressed in a proportion of pre-menopausal women receiving TAMOPLEX for the treatment of breast cancer.

Secondary tumours and carcinomas:

A number of second 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 TAMOPLEX. No causal link has been established and the clinical significance of these observations remains unclear.

Hepatocarcinogenicity of TAMOPLEX has been reported in long-term carcinogenicity studies with rodents. Cases of hepatocellular carcinoma have also been reported in clinical TAMOPLEX studies. There are also study results suggesting an increased incidence of gastrointestinal cancers in association with TAMOPLEX treatment in breast cancer patients. Liver laboratory values of patients on TAMOPLEX treatment should be regularly monitored.
Assessment of triglycerides in serum may also be advisable.

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

Anticoagulants:

When TAMOPLEX is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect with risk of bleeding may occur. Where such co-administration is initiated a reduction of anticoagulant dosage and careful monitoring of the patient is recommended (see **section 4.5**).

Endometrial changes:

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

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.

Thromboembolic events:

There is evidence that treatment with TAMOPLEX 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. Close monitoring is recommended for patients who present a risk for thromboembolic events.

Venous thromboembolism (VTE):

In patients with breast cancer, prescribers should obtain careful histories with respect to the patient's personal and family history of VTE. If suggestive of a prothrombotic risk, patients should be screened for thrombophillic factors.

Patients who test positive should be counselled regarding their thrombotic risk. The decision to use TAMOPLEX in these patients should be based on the overall risk to the patient. In selected patients, the use of

TAMOPLEX with prophylactic anticoagulation may be justified.

The risk of VTE is further increased by severe obesity, increasing age and all other factors for VTE. The risks and benefits should be carefully considered for all patients before treatment with TAMOPLEX. In patients with breast cancer, this risk is also increased by concomitant chemotherapy (see **section 4.5**). Long-term anticoagulant prophylaxis may be justified for some patients with breast cancer who have multiple risk factors for VTE.

Surgery and immobility: For patients being treated for infertility, tamoxifen should be stopped at least 6 weeks before surgery or long-term immobility (when possible) and re-started only when the patient is fully mobile. For patients with breast cancer, TAMOPLEX treatment should only be stopped if the risk of TAMOPLEX-induced thrombosis clearly outweighs the risks associated with interrupting treatment. All patients should receive appropriate thrombosis prophylactic measures and should include graduated compression stockings for the period of hospitalisation, early ambulation, if possible, and anticoagulant treatment.

If any patient presents with VTE, TAMOPLEX should be stopped immediately and appropriate anti-thrombosis measures initiated. In patients being treated for infertility, TAMOPLEX should not be re-started unless there is a compelling alternative explanation for their thrombotic event. In patients receiving TAMOPLEX for breast cancer, the decision to re-start TAMOPLEX should be made with respect to the overall risk for the patient. In selected patients with breast cancer, the continued use of TAMOPLEX with prophylactic anticoagulation may be justified.

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

CYP2D6 poor metabolisers/interactions:

Literature reports show that CYP2D6 poor metabolisers have a lowered plasma level of endoxifen, one of the most important active metabolites of tamoxifen.

Concomitant medications 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 TAMOPLEX treatment (see **section 4.5**).
Available clinical data suggests that patients who are homozygote for non-functional CYP2D6 alleles, may experience a reduced effect of TAMOPLEX.

Complications during breast reconstruction:

In delayed microsurgical breast reconstruction, TAMOPLEX may increase the risk of microvascular flap complications.

Changes in calcium metabolism and patients with bone metastases:

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 TAMOPLEX treatment, with subsequent resumption of therapy at a reduced dosage, with gradual increase to the full dose. Hypercalcaemia may occur in some breast cancer patients with bone metastases within a few weeks of starting treatment with TAMOPLEX. Patients with bone metastases should be closely monitored during the first weeks of therapy; if hypercalcaemia does occur appropriate measures should be taken and TAMOPLEX should be withdrawn. Serum calcium should be checked regularly.

Premenopausal patients:

Must be examined before TAMOPLEX treatment to exclude the possibility of pregnancy. Moreover, TAMOPLEX may occasionally increase oestradiol plasma concentrations and may induce ovulation, exposing patients at risk of pregnancy. In pre-menopausal woman, TAMOPLEX completely suppresses menstruation and cystic ovarian swelling may develop.

Leucopenia or thrombocytopenia:

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

Visual disturbances:

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

Lactose:

Contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take TAMOPLEX.

4.5 Interaction with other medicines and other forms of interaction:

When TAMOPLEX is used in combination with coumarin-type anticoagulants (e.g. warfarin), a significant increase in anticoagulant effect with the risk of bleeding may occur. TAMOPLEX and coumarin-type anticoagulants (e.g. warfarin) should be used concomitantly with caution, and INR (International Normalised Ratio) should be closely monitored (see **section 4.4**).
Platelet aggregation inhibitors should not be combined with TAMOPLEX in order to avoid bleeding during the possible thrombocytopenic period.

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

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

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 TAMOPLEX (see **section 4.4**).

The serum levels of TAMOPLEX 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 TAMOPLEX and its metabolites.

Various degrees of oestrogen effects on Papanicolau (PAP) smears have been reported in postmenopausal patients who are receiving TAMOPLEX.

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

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

Co-administration with cytotoxic medicines increases the risk for thromboembolic events. Because of this increase in risk of VTE, thrombosis prophylaxis should be considered for these patients for the period of concomitant chemotherapy.

Concomitant use of mitomycin (even in small doses) and TAMOPLEX should be avoided, since there is an increased risk for haemolytic-uremic syndrome, anaemia and thrombocytopenia.

TAMOPLEX is mainly metabolised by CYP3A4. Caution is required when TAMOPLEX is co-administered with known CYP3A4 enzyme inhibitors or inducers (e.g. rifampicin).

Pharmacokinetic interaction with CYP2D6 inhibitors, showing a reduction in plasma levels of the active tamoxifen metabolite, endoxifen, has been reported in the literature.

Reduced efficacy of tamoxifen as found in TAMOPLEX has been reported with concomitant usage of some SSRI antidepressants (e.g. paroxetine) in some studies. As a reduced effect of tamoxifen cannot be excluded, co-administration of TAMOPLEX with potent CYP2D6 inhibitors (e.g. paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should whenever possible be avoided.

4.6 Fertility, pregnancy and lactation:

Pregnancy:

TAMOPLEX should not be given during pregnancy and should be used with caution in women with functioning ovaries (see **section 4.3**).

Premenopausal patients must be carefully examined before TAMOPLEX treatment to exclude pregnancy. Women should be appraised of the potential risks to the foetus, should they become pregnant whilst taking TAMOPLEX or within nine months of cessation of TAMOPLEX therapy.

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 TAMOPLEX.

Lactation:

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 not recommended during TAMOPLEX treatment (see **section 4.3**).
Limited data suggest that tamoxifen and its active metabolites are excreted and accumulate over time in human milk; therefore, TAMOPLEX is not recommended during breastfeeding. The decision to either discontinue nursing or discontinue TAMOPLEX should take into account the importance of TAMOPLEX to the mother.

Contraception in males and females:

Due to the genotoxic potential of tamoxifen, women of childbearing potential should use effective contraceptive measures while being treated with TAMOPLEX and for 9 months following completion of treatment.
Men are recommended to use effective contraceptive measures and to not father a child while receiving TAMOPLEX and for 6 months following completion of treatment.

4.7 Effects on ability to drive and use machines:

TAMOPLEX may cause fatigue and visual disturbances and this may affect the ability to drive or operate machinery.

4.8 Undesirable effects:

SYSTEM ORGAN CLASS:	**FREQUENCY:**	**UNDESIRABLE EFFECTS:**
Neoplasms benign and malignant (including cysts and polyps):	*Frequent:*	Uterine fibroids, endometrial cancer
	Less frequent:	Uterine sarcoma (mostly malignant mixed Mullerian tumours), tumour flare
	Frequency unknown:	Hepatocellular cancer
Blood and the lymphatic system disorders:	*Frequent:*	Anaemia
	Less frequent:	Haemorrhagic episodes, neutropenia, thrombocytopenia, leukopenia, agranulocytosis. *(Transient falls in platelet count, usually up to 80 000 - 90 000, but occasionally lower, have been reported in patients taking* TAMOPLEX *for breast cancer).*
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)

	Frequency unknown:	Anorexia	
Psychiatric disorders:	*Frequency unknown:*	Depression, confusion	
Nervous system disorders:	*Frequent:*	Ischaemic cerebrovascular events, stroke, headache, light-headedness, sensory disturbances (including paraesthesia and dysgeusia)	
	Less frequent:	Optic neuritis	
	Frequency unknown:	Dizziness	
Eye disorders:	*Frequent:*	Cataracts, retinopathy	
	Less frequent:	Visual disturbances, corneal changes, optic neuropathy	
Vascular disorders:	*Frequent:*	Hot flushes, thromboembolic events (including deep vein thrombosis, microvascular thrombosis and pulmonary embolism)	
	Frequency unknown:	Oedema, thrombophlebitis, thromboembolism, cerebrovascular accidents	
Respiratory, thoracic and mediastinal disorders:	*Less frequent:*	Interstitial pneumonitis	
	Frequency unknown:	Cough	
Gastrointestinal disorders:	*Frequent:*	Gastrointestinal upsets (such as nausea and vomiting), diarrhoea, constipation	
	Less frequent:	Pancreatitis	

	Frequency unknown:	Abdominal cramps	
Hepato-biliary disorders:	*Frequent:*	Changes in liver enzymes, development of fatty liver	
	Less frequent:	Severe hepatic abnormalities (including hepatic necrosis, hepatic failure), cirrhosis, cholestasis, hepatitis, jaundice, liver cell necrosis, liver cell damage, liver failure	
	Frequency unknown:	Hepatotoxicity, alterations of liver function parameters, serum lipid changes, steatosis	
Skin and subcutaneous tissue disorders:	*Frequent:*	Rashes, dry skin, alopecia	
	Less frequent:	Stevens-Johnson syndrome, cutaneous lupus erythematosus, angioedema, cutaneous vasculitis, bullous pemphigoid, erythema multiforme, toxic epidermal necrolysis	
	Frequency unknown:	Exacerbation of hereditary angioedema	
Musculoskeletal and connective tissue disorders:	*Frequent:*	Leg cramps, myalgia	
	Frequency unknown:	Bone pain	
	Frequent:	Vaginal bleeding or discharge, pruritus vulvae, menstrual irregularities	

Reproductive system and breast disorders:		(including amenorrhoea), endometrial carcinoma, endometrial changes (including hyperplasia and polyps)
	Less frequent:	Uterine sarcomas, endometriosis, cystic ovarian swelling, vaginal polyps
Congenital, familial and genetic disorders:	*Less frequent:*	Porphyria cutanea tarda
General disorders and administration site conditions:	*Frequent:*	Fatigue
	Frequency unknown:	Oedema, weight gain, tumour pain
Investigations:	*Frequent:*	Elevated triglycerides
Injury, poisoning and procedural complications:	*Less frequent:*	Recall phenomenon

When side effects are severe, it is sometimes possible to control them by a simple reduction of dosage without loss of control of the disease. If side effects do not respond to this measure, it may be necessary to stop treatment with TAMOPLEX.

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:

See undesirable effects. There is no specific antidote. Treatment should be symptomatic and supportive.

Plasma clearance is reported to be biphasic and the terminal half-life may be longer than 7 days.

An overdosage would be expected to cause enhancement of the anti-oestrogenic adverse reactions. There have been reports in the literature that TAMOPLEX given at several times the standard dose may be associated with prolongation of the QT interval of an ECG.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

A 21.12 Hormone inhibitor

ATC code: L02BA01

Mechanism of action:

Tamoxifen is anti-oestrogenic and binds to oestrogen receptors in a fashion similar to that of oestradiol, and competes with oestrogen for binding sites in 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.

5.2 Pharmacokinetic properties:

Absorption:

After oral administration, tamoxifen is well absorbed with peak plasma concentrations of tamoxifen occurring within 4 to 7 hours.

Steady state levels are reached after 4 to 6 weeks.

Distribution:

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

Elimination:

Tamoxifen is metabolised mainly by CYP3A4 & CYP2D6 to N-desmethyltamoxifen and 4-hydroxytamoxifen

respectively. Tamoxifen has a half-life of 7 days, while the half-life of N-desmethyltamoxifen and 4-hydroxytamoxifen 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.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

The other ingredients in TAMOPLEX are:

Colloidal anhydrous silica

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Potato starch

Polyvidone

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

5 years

6.4 Special precautions for storage:

Store at or below 25 ºC. Keep well closed and protect from light.

Keep blister in carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container:

TAMOPLEX: White plastic containers of 30, 100 and 250 tablets. 3 blister strips of 10 tablets packed in a unit carton.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product:

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd,

Maxwell Office Park,

Magwa Crescent West,

Waterfall City,

Midrand,

Gauteng,

South Africa,

2090

8. REGISTRATION NUMBER:

34/21.12/0067

9. DATE OF FIRST AUTHORISATION:

13 December 2001

10. DATE OF REVISION OF TEXT:

14 February 2024