PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE
TAMOXAL 10 (film-coated tablets)
TAMOXAL 20 (film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each TAMOXAL 10 film-coated tablet contains tamoxifen citrate equivalent to 10 mg tamoxifen.
Each TAMOXAL 20 film-coated tablet contains tamoxifen citrate equivalent to 20 mg tamoxifen.
Tamoxifen is the trans isomer of 1-[4-(2-dimethylamino-ethoxy)phenyl]-1,2 diphenyl-1-butene.
Excipient with known effect:
Each TAMOXAL 10 mg film-coated tablet contains sugar (lactose monohydrate 71,3 mg).
Each TAMOXAL 20 mg film-coated tablet contains sugar (lactose monohydrate 142,6 mg).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
TAMOXAL 10: Uniform, white, round, biconvex, film coated tablet.
Diameter of 7,0 - 7,3mm. Height of 3,4 - 3,7mm.
TAMOXAL 20: Uniform, white, round, biconvex, film coated tablet bisected by a score notch on one face.
Diameter of 9,0 - 9,3 mm. Height of 3,7 - 4,1 mm.

4 CLINICAL PARTICULARS
4.1. Therapeutic indications
TAMOXAL is indicated for the treatment of breast cancer.

4.2. Posology and method of administration
Adults
The dose range is 20 mg to 40 mg given either in divided doses twice daily or as a single dose, once daily.

Use in the Elderly
Dosage as above.

Paediatric population
The use of tamoxifen is not recommended in children. The safety and efficacy of tamoxifen in children has not yet been established.

4.3 Contraindications
- Do not give tamoxifen during pregnancy or lactation.
- ***Lactation:*** It is not known if tamoxifen is excreted in human milk, and therefore the medicine is not recommended during lactation (see section 4.6 Fertility, pregnancy and lactation).
- Pre-menopausal patients must be carefully examined before commencing treatment to exclude the possibility of pregnancy.
- Hypersensitivity to tamoxifen or any of the other ingredients of this formulation.
- Concurrent anastrozole therapy.

4.4 Special warnings and precautions for use
Menstruation is suppressed in a proportion of premenopausal women receiving tamoxifen for the treatment of breast cancer.

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

There are several factors that influence the risk of developing endometrial cancer, with the majority of risk factors affecting oestrogen levels. Therefore, tamoxifen treatment may increase the incidence of endometrial cancer. In addition, other risk factors include obesity, nulliparity, diabetes mellitus, polycystic ovary syndrome and oestrogen-only HRT. There is also the general risk for endometrial cancer with increasing age. Any patient receiving or having previously received tamoxifen who reports 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.

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 tamoxifen. No causal link has been established and the clinical significance of these observations remains unclear.

Venous thromboembolism (VTE):
- A two- to three-fold increase in the risk for VTE has been demonstrated in healthy tamoxifen-treated women (see section 4.8).
- 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 thrombophilic factors. Patients who test positive should be counselled regarding their thrombotic risk. The decision to use tamoxifen in these patients should be based on the overall risk to the patient. In selected patients, the use of tamoxifen with prophylactic anticoagulation may be justified (see section 4.5).
- The risk of VTE is further increased by severe obesity, increasing age and all other risk factors for VTE. The risks and benefits should be carefully considered for all patients before treatment with tamoxifen. 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: Tamoxifen treatment should only be stopped if the risk of tamoxifen-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, tamoxifen should be stopped immediately and appropriate anti-thrombosis measures initiated. The decision to re-start tamoxifen should be made with respect to the overall risk for the patient. In selected patients with breast cancer, the continued use of tamoxifen 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.

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

In the literature, it has been shown that CYP2D6 poor metabolisers have a lowered plasma level of endoxifen, one of the most important active metabolites of tamoxifen (see section 5.2).
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 tamoxifen treatment (see section 4.5 and 5.2).

Radiation recall has been reported very rarely in patients on tamoxifen who have received prior radiotherapy. There action is usually reversible upon temporary cessation of therapy and re-challenge may result in a milder reaction. Treatment with tamoxifen was continued in most cases.

Toxic epidermal necrolysis
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 tamoxifen 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, tamoxifen 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 tamoxifen, treatment with tamoxifen must not be restarted in this patient at any time.

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

Lactose intolerance:
TAMOXAL contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take TAMOXAL.

4.5 Interaction with other medicines and other forms of interaction
When tamoxifen 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, reduction of anticoagulant dosage and careful monitoring of the patient is recommended.

When tamoxifen is used in combination with cytotoxic agents, there is increased risk of thromboembolic events occurring (see also sections 4.4 and 4.8). Because of this increase in risk of VTE, thrombosis prophylaxis should be considered for these patients for the period of concomitant chemotherapy.

The use of tamoxifen in combination with anastrozole as adjuvant therapy has not shown improved efficacy compared with tamoxifen alone.

As tamoxifen is metabolised by cytochrome P450 3A4, care is required when co- administering with medicines, such as rifampicin, known to induce this enzyme as tamoxifen levels may be reduced. The clinical relevance of this reduction is unknown.

Pharmacokinetic interaction with CYP2D6 inhibitors, showing a reduction in plasma level of an active tamoxifen metabolite, 4-hydroxy-Ndesmethyl-tamoxifen (endoxifen), has been reported in the literature.

Pharmacokinetic interaction with CYP2D6 inhibitors, showing a 65-75% reduction in plasma levels of one of the more active forms of the medicine, i.e. endoxifen, has been reported in the literature. Reduced efficacy of tamoxifen 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 with potent CYP2D6 inhibitors (e.g. paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should whenever possible be avoided (see section 4.4 and 5.2).

4.6 Fertility, pregnancy and lactation
Women of childbearing potential / Contraception in males and females
Women should be advised not to become pregnant whilst taking tamoxifen and for nine months following the cessation of therapy and should use barrier or other non-hormonal contraceptive methods if sexually active. Premenopausal patients 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 tamoxifen or within nine months of cessation of therapy.

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

Reproductive toxicology studies in rats, rabbits and monkeys have shown no teratogenic potential.

In rodent models of foetal reproductive tract development, tamoxifen 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 1000 risk of developing clear-cell carcinoma of the vagina or cervix.

Breastfeeding
Limited data suggest that tamoxifen and its active metabolites are excreted and accumulate over time in human milk, therefore the medicine is not recommended during breast-feeding. The decision either to discontinue nursing or discontinue tamoxifen should take into account the importance of the medicine to the mother.

Fertility
There is no human data on the effect of tamoxifen on fertility.

4.7. Effects on ability to drive and use machines
Tamoxifen is unlikely to impair the ability of patients to drive or operate machinery. However, fatigue has been reported with the use of tamoxifen and caution should be observed when driving or using machinery while such symptoms persist.

4.8. Undesirable effects
Tabulated list of adverse reactions

Adverse Drug Reactions (ADR) by System Organ Class (SOC) and Frequency

System Organ Class	Frequent	Less frequent	Frequency Unknown
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Uterine fibroids	Endometrial cancer, Uterine Sarcoma (mostly malignant mixed Mullerian tumours),Tumour Flare	
Blood and Lymphatic System Disorders	Anaemia	Thrombocytopenia, Leucopenia, Neutropenia, Agranulocytosis	
Immune System Disorders	Hypersensitivity reactions		
Metabolism And Nutrition Disorders	Fluid retention	Hypercalcaemia (in patients with bony metastases)	
Nervous System Disorders	Ischaemic cerebrovascular events, Headache, Light headedness, Sensory disturbances (including paraesthesia and dysgeusia)	Optic neuritis	
Eye disorders	Cataracts, Retinopathy	Visual disturbances, Corneal changes, Optic neuropathy	
Vascular disorders	Hot flushes	Thromboembolic events (including deep vein thrombosis, microvascular thrombosis and pulmonary embolism)	
Respiratory, Thoracic and Mediastinal Disorders		Interstitial pneumonitis	
Gastrointestinal Disorders	Nausea, Vomiting, Diarrhoea, Constipation	Pancreatitis	
Hepatobiliary Disorders	Changes in liver enzymes, Fatty liver	Cirrhosis of the liver, Hepatitis, Cholestasis, Hepatic failure, Hepatocellular injury, Hepatic necrosis	
Skin and Subcutaneous Tissue Disorders	Skin Rash, Alopecia	Angioedema, Steven-Johnsons syndrome, Cutaneous vasculitis, Bullous pemphigoid, Erythema multiforme, Cutaneous lupus erythematosus	Exacerbation of hereditary angioedema
Musculoskeletal and Connective Tissue Disorders	Leg cramp, Myalgia		
Reproductive System and Breast Disorders	Vaginal bleeding, Vaginal discharge Pruritis vulvae, Endometrial changes (including hyperplasia and polyps)	Endometriosis, Cystic ovarian swelling, Vaginal polyps	
Congenital, Familial and Genetic Disorders		Porphyria cutanea tarda	
General Disorders and Administration Site Conditions	Fatigue		
Investigations	Elevated triglycerides		
Injury, Poisoning and Procedural Complications		Radiation Recall	

Description of selected adverse reactions
Side effects can be classified as either due to the pharmacological action of the medicine, e.g. hot flushes, vaginal bleeding, vaginal discharge, pruritus vulvae and tumour flare, or as more general side effects, e.g. gastrointestinal intolerance, headache, light-headedness and occasionally, fluid retention and alopecia.
When side effects are severe, it may be possible to control them by a simple reduction of dosage (to not less than 20 mg/day) without loss of control of the disease. If side effects do not respond to this measure, it may be necessary to stop the treatment.

Skin rashes (including rare reports of erythema multiforme, Stevens- Johnson syndrome, cutaneous vasculitis and bullous pemphigoid) and commonly hypersensitivity reactions including angioedema have been reported.

Uncommonly, patients with bony metastases have developed hypercalcaemia on initiation of therapy.

Cases of visual disturbances, including rare reports of corneal changes, and common reports of retinopathy have been described in patients receiving tamoxifen therapy. Cataracts have been reported commonly in association with the administration of tamoxifen.

Cases of optic neuropathy and optic neuritis have been reported in patients receiving tamoxifen and, in a small number of cases, blindness has occurred.

Sensory disturbances (including paraesthesia and dysgeusia) have been reported commonly in patients receiving tamoxifen.

Uterine fibroids, endometriosis and other endometrial changes including hyperplasia and polyps have been reported.

Falls in platelet count, usually to 80,000 to 90,000 per cu mm but occasionally lower, have been reported in patients taking tamoxifen for breast cancer.

Leucopenia has been observed following the administration of tamoxifen, sometimes in association with anaemia and/ or thrombocytopenia. Neutropenia has been reported on rare occasions; this can sometimes be severe, and very rarely cases of agranulocytosis have been reported.

There is evidence of ischaemic cerebrovascular events and thromboembolic events, including deep vein thrombosis, microvascular thrombosis and pulmonary embolism, occurring commonly during tamoxifen therapy (see sections 4.3, 4.4 and 4.5). When tamoxifen is used in combination with cytotoxic agents, there is an increased risk of thromboembolic events occurring.

Leg cramps and myalgia have been reported commonly in patients receiving tamoxifen.
Uncommonly, cases of interstitial pneumonitis have been reported.

Tamoxifen has been associated with changes in liver enzyme levels and with a spectrum of more severe liver abnormalities which in some cases were fatal, including fatty liver, cholestasis and hepatitis, liver failure, cirrhosis, and hepatocellular injury (including hepatic necrosis).

Commonly, elevation of serum triglyceride levels, in some cases with pancreatitis, may be associated with the use of tamoxifen.

Cystic ovarian swellings have rarely been observed in women receiving tamoxifen.

Vaginal polyps have rarely been observed in women receiving tamoxifen.

Cutaneous lupus erythematosus has been observed very-rarely in patients receiving tamoxifen.

Porphyria cutanea tarda has been observed very-rarely in patients receiving tamoxifen.

Fatigue has been reported very commonly in patients taking tamoxifen.

Radiation Recall has been observed very rarely in patients receiving tamoxifen.

Uncommonly incidences of endometrial cancer and rare instances of uterine sarcoma (mostly malignant mixed Mullerian tumours) has been reported in association with tamoxifen treatment.

Paediatric population
The use of tamoxifen is not recommended in children. The safety and efficacy of tamoxifen in children has not yet been established.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://sahpra.org.za/wp-content/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf.
Suspected adverse reactions can also be reported directly to the Holder of the Certificate of Registration (HCR) via Patientsafety.sacg@novartis.com.

4.9 Overdose
On theoretical grounds, an over dosage would be expected to cause enhancement of the pharmacological side effects mentioned above. Observations in animals show that extreme over dosage (100 - 200 times recommended daily dose) may produce oestrogenic effects.

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

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

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic properties
Pharmacological classification: A 21.12 Hormone inhibitors
Pharmacotherapeutic group: Anti-oestrogens. ATC code: L02BA01.

Tamoxifen is a non-steroidal, triphenylethylene-based medicine which displays a complex spectrum of oestrogen antagonist and oestrogen agonist-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 of the order of 10 - 20%. Tamoxifen does not adversely affect bone mineral density in postmenopausal women.

CYP2D6 polymorphism status may be associated with variability in clinical response to tamoxifen. The poor metaboliser status may be associated with reduced response. The consequences of the findings for the treatment of CYP2D6 poor metabolisers, have not been fully elucidated.

CYP2D6 genotype
Available clinical data suggest that patients, who are homozygote for non-functional CYP2D6 alleles, may experience reduced effect of tamoxifen in the treatment of breast cancer.

5.2. Pharmacokinetic properties
Absorption
Following oral administration, tamoxifen is absorbed with maximum serum concentrations occurring within 4 to 7 hours.

Distribution
Steady state concentrations (about 300 ng/ ml) are achieved after four weeks treatment with 40 mg daily. The medicine is highly protein bound to serum albumin (> 99 %).

Biotransformation
Metabolism is by hydroxylation, demethylation and conjugation, giving rise to several metabolites which have a similar pharmacological profile to the parent compound and thus contribute to the therapeutic effect.

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

Elimination
Excretion occurs primarily via the faeces. An elimination half-life for tamoxifen itself has been calculated at approximately seven days, whereas that for N-desmethyltamoxifen, the principal circulating metabolite, is 14 days.

5.3 Preclinical safety data
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.
Tamoxifen is a medicine on which extensive clinical experience has been obtained.

6. PHARMACEUTICAL PARTICULARS
6.1. List of excipients
Lactose Monohydrate
Microcrystalline Cellulose
Magnesium Stearate
Povidone (Kollidon 25)
Sodium Starch Glycollate
Coating:
Opadry white* composed of:
- *Hypromellose*
- *Lactose monohydrate*
- *Macrogol 4000*
- *Titanium dioxide*

*coating mixture can alternatively be composed of the single ingredients Lactose Monohydrate 36% w/w, Titanium dioxide 26% w/w, Hypromellose 28% w/w and Macrogol 4000 10% w/w; all single components comply to the specification of Ph. Eur. (current version).

6.2. Incompatibilities
Not applicable.

6.3. Shelf life
24 months.
Store below 25 °C

6.4. Special precautions for storage
Sensitivity to light. Store in the original package

6.5. Nature and contents of container
PVDC coated PVC/aluminium blisters. 10 tablets per blister strip, 3 blister strips per carton (30's)

6.6. Special precautions for disposal and other handling
No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Trinity Pharma (Pty) Ltd
3 Gwen Lane, 4th Floor, Sandton, 2031.
Contact No.: +27 (0)10 594 5610
PV Email Address: pv@trinitypharma.co.za

8. REGISTRATION NUMBERS
TAMOXAL 10: 33/21.12/0517
TAMOXAL 20: 33/21.12/0518

9. DATE OF FIRST AUTHORISATION
23 September 2005

10. DATE OF REVISION OF THE TEXT
02 February 2021

TRINITY PHARMA