SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medical Product

Drug Product	**:**	Tamoxifen Citrate Tablets USP 20 mg
Generic Name	**:**	Tamoxifen Citrate USP
Strength	**:**	Each uncoated tablet contains, 20 mg of Tamoxifen per tablet
Description	**:**	White to off White circular shaped flat, beveled edge uncoated tablets, scored on one side and embossed "20" on other.

2. Quality and Quantitative Composition

Each uncoated tablet contains:

Tamoxifen Citrate USP Eq. to Tamoxifen	20 mg
Excipients	qs.

QUALITATIVE AND QUANTITATIVE FORMULA

Name of Ingredients
Tamoxifen citrate*
Mannitol
Corn Starch
Polacrilin Potassium (Doshion P544)
Croscarmellose Sodium
Povidone (P.V.P. K-30)
Purified Talc
Magnesium Stearate
Polacrilin Potassium (Doshion P544)
Colloidal silicon dioxide
Purified Water

3. Pharmaceutical form

Uncoated tablets for oral use only.

4. Clinical Particulars

4.1 Therapeutic Indications

Metastatic Breast Cancer

Tamoxifen citrate is effective in the treatment of metastatic breast cancer in women and men. In premenopausal women with metastatic breast cancer, Tamoxifen citrate is an alternative to oophorectomy or ovarian irradiation.

Adjuvant Treatment of Breast Cancer

Tamoxifen citrate is indicated for the treatment of node-positive breast cancer in women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation.
Tamoxifen citrate reduces the occurrence of contralateral breast cancer in patients receiving adjuvant Tamoxifen citrate therapy for breast cancer.

Ductal Carcinoma in Situ (DCIS)

In women with DCIS, following breast surgery and radiation, Tamoxifen citrate is indicated to reduce the risk of invasive breast. The decision regarding therapy with Tamoxifen citrate for the reduction in breast cancer incidence should be based upon an individual assessment of the benefits and risks of Tamoxifen citrate therapy.

Reduction in Breast Cancer Incidence in High Risk Women

Tamoxifen citrate is indicated to reduce the incidence of breast cancer in women at high risk for breast cancer. This effect was shown in a study of 5 years planned duration with a median follow-up of 4.2 years. Twenty-five percent of the participants received drug for 5 years. The longer-term effects are not known.

4.2 Posology and method of administration

Adults:

I) **Breast Cancer:** The recommended daily dose of Tamoxifen is normally 20 mg. No additional benefit, in terms of delayed recurrence or improved survival in patients, has been demonstrated with higher doses. Substantive evidence supporting the use of treatment with 30-40 mg per day is not available, although these doses have been used in some patients with advanced disease.

II) **Anovulatory Infertility:** The possibility of pregnancy must be excluded before the commencement of treatment, whether initial or subsequent. In women with regular menstruation but with anovular cycles, treatment should commence with 20 mg daily in either one or two doses administered on the second, third, fourth and fifth days of the menstrual cycle. In unsuccessful cases further courses may be given during subsequent menstrual periods, increasing the dosage to 20 mg then 40 mg twice daily.
In women with irregular menstruation, the commencement of treatment may take place on any day. If this initial course is not successful then a further course may be initiated after an interval of 45 days with the higher dosage level (20 mg to 40 mg twice daily).

If a patient responds with menstruation then the next course of treatment should be initiated on the second day of the cycle.

III) **Primary prevention of breast cancer:**Tamoxifen treatment for the primary prevention of breast cancer should only be initiated by a medical practitioner experienced in prescribing for this indication, and as part of a shared care pathway arrangement, with appropriate patient identification, management and follow up.

The recommended dose is 20 mg daily for 5 years for those women at moderate or high risk. There are insufficient data to support a higher dose or longer period of use.

Before commencing treatment, an assessment of the potential benefits and risks is essential, including calculating a patient's risk of developing breast cancer according to local guidelines and risk assessment tools. Validated algorithms are available that calculate breast cancer risk based on features such as age, family history, genetic factors, reproductive factors and history of breast disease.

The use of Tamoxifen should be as part of a program including regular breast surveillance tailored to the individual woman, taking into account her risk of breast cancer.

Elderly:

The adult dosage range has been used in elderly patients with breast cancer and in some of these patients it has been used as sole therapy.

Paediatric population:

The use of tamoxifen is not recommended in children and adolescents.

Hepatic Impairment

Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed.

Renal Impairment

Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

Method of administration

Oral Administration, Tamoxifen may be taken with or without food.

If a dose of tamoxifen is missed, administer the dose as soon as possible. If it is almost time for the next dose, skip the missed dose and administer the next dose at the regularly scheduled time.

4.3 Contraindications

- In pregnancy Pre-menopausal patients should have pregnancy excluded before treatment is commenced.
- In concurrent anastrozole therapy
- Treatment for infertility: Tamoxifen should not be used in patients with a personal or family history of confirmed idiopathic venous thromboembolic events or a known genetic defect.
- Primary prevention of breast cancer

Tamoxifen should not be used in:

- Women with a history of deep vein thrombosis or pulmonary embolus.
- Women who require concomitant coumarin-type anticoagulant therapy

4.4 Special Warnings and precautions for use

Before taking tamoxifen, tell your doctor or pharmacist if you are allergic to it; or if you have any other allergies. This product may contain inactive ingredients, which can cause allergic reactions or other problems. Talk to your pharmacist for more details.

Before using this medication, tell your doctor or pharmacist your medical history, especially of: blood clots (e.g., deep vein thrombosis, pulmonary embolism, stroke), high cholesterol/triglycerides, limited or no ability to walk (immobility), diabetes, high blood pressure, smoking, cataracts, liver disease.

Before having surgery (especially breast reconstruction), tell your doctor or dentist about all the products you use (including prescription drugs, nonprescription drugs, and herbal products).

Tell your doctor if you are pregnant or plan to become pregnant. You should not become pregnant while using tamoxifen. Tamoxifen may harm an unborn baby. Women using this medication should ask about reliable non-hormonal forms of birth control (such as condoms, diaphragms with spermicide) during treatment and for 2 months after stopping treatment. Men using this medication should ask about reliable forms of birth control during treatment and for 6 months after stopping treatment. If you or your partner become pregnant, talk to your doctor right away about the risks and benefits of this medication.

It is unknown if this medication passes into breast milk. Because of the possible risk to the infant, breast-feeding is not recommended while using this drug and for 3 months after stopping treatment. Consult your doctor before breast-feeding.

4.5 Interaction with other medicinal products and other form of interactions

When tamoxifen is used in combination with coumarin-type anticoagulants, such as warfarin, a significant increase in anticoagulant effect may occur. Patients taking coumarin-type anticoagulants will require careful monitoring, including initiation or withdrawal of tamoxifen.

Concurrent use with cytotoxic agents, for the treatment of breast cancer, increases the risk of thromboembolic events occurring. 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 drugs, 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 65-75% reduction in plasma levels of one of the more active forms of the drug, 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.

Primary prevention of breast cancer risk

In women receiving Tamoxifen for the primary prevention of breast cancer, the use of coumarin type anticoagulants is contraindicated.

There is some evidence that hormone replacement therapy may reduce the effectiveness of Tamoxifen, and the concomitant use of Tamoxifen and oral hormonal contraceptives is not recommended.

4.6 Pregnancy and lactation

Pregnancy

Tamoxifen is contra-indicated in pregnancy. There have been a small number of reports of spontaneous abortions, birth defects and foetal deaths after women have taken tamoxifen although no causal relationship has been established.

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, ethinylestradiol, clomifene and diethylstilbestrol (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.
Only a small number of pregnant women have been exposed to tamoxifen. Such exposure has not been reported to cause subsequent vaginal adenosis or clear-cell carcinoma of the vagina or cervix in young women exposed in utero to tamoxifen.

Women should be advised not to become pregnant whilst taking tamoxifen and should use barrier or other non-hormonal contraceptive methods if sexually active. Pre-menopausal 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 two months of cessation of therapy.

Breast-feeding

It is unknown whether tamoxifen is excreted in human milk and therefore the drug is not recommended during lactation. The decision either to discontinue nursing or discontinue tamoxifen should take into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machine

Tamoxifen has no or negligible influence on the ability 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

Unless specified, the following frequency categories were calculated from the number of adverse events reported in a large phase III study conducted in 9366 postmenopausal women patients with operable breast cancer treated for 5 years and, unless specified, no account was taken of the frequency within the comparative treatment group or whether the investigator considered it to be related to study medication. The safety findings in the breast cancer prevention trials appeared consistent overall with the established safety profile of Tamoxifen.

	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare ≥1/10,000 to <1/1,000)	Very rare (<1/10,000) including isolated reports.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Uterine fibroids	Endometrial cancer	Uterine sarcoma (mostly malignant mixed Mullerian tumours)[a] Tumour flare[a]	
Blood and lymphatic system disorders		Anaemia	Thrombocytopenia Leucopenia, in association with anaemia and/or thrombocytopenia.	Neutropenia[a] (this can sometimesbe severe) Agranulocytosis[a] Transient falls in platelet counts usually between 80,000 - 90,000 per cu mm but occasionally lower have been reported in patients taking tamoxifen for breast cancer	The tendency towards thrombophlebitis may increase and transient thrombocytopenia may occur.
Immune system disorders		Hypersensitivity reactions			
Metabolism and nutrition disorders	Fluid retention		Hypercalcaemia (in patients with bone metastases) on initiation of therapy		

Nervous system disorders		Ischaemic cerebrovascular events Headache Light-headedness Sensory disturbances (including paraesthesia and dysgeusia)		Optic neuritis*	
Eye disorders		Cataracts[$] Retinopathy[$]	Visual disturbance[$]	Corneal changes[$] Optic neuropathy[a] *	
Vascular disorders	Hot flushes	Thrombo-embolic events (including deep vein thrombosis and microvascular thrombosis). Risks are increased when tamoxifen is used in combination with cytotoxic agents			
Respiratory thoracic and mediastinal disorders		Thrombo-embolic events (including pulmonary embolism). Risk is increased when tamoxifen is used in combination with cytotoxic agents	Interstitial pneumonitis		
Gastrointestinal disorders	Nausea	Vomiting Diarrhoea Constipation	Pancreatitis[%]		
Hepatobiliary disorders		Changes in liver enzyme Fatty liver[&]	Cirrhosis of the liver[&]	Cholestasis[a &] Hepatitis [&] Hepatic failure[a &]	

				Hepatocellular injury[a &] Hepatic necrosis[a &]	
Skin and subcutaneous tissue disorders	Skin rash	Alopecia		Angioedema Stevens-Johnson syndrome[a] Cutaneous vasculitis[a] Bullous pemphigoid[a] Erythema multiforme[a]	Cutaneous lupus erythematosus[b]
Musculoskeletal and connective tissue disorders		Leg cramp Myalgia			
Reproductive system and breast disorders	Vaginal bleeding Vaginal discharge	Pruritus vulvae Endometrial changes (including hyperplasia and polyps)		Suppression of menstruation in premenopausal women Endometriosis[a] Cystic ovarian swelling[a] Vaginal polyps	
Congenital, familial and genetic disorders					Porphyria cutanea tarda[b]
General disorders and administration site conditions	Fatigue	Tumour pain			
Investigations		Increase of serum triglyceride[%]			
Injury, poisoning and procedural complications					Radiation Recall[b]

[a] This adverse drug reaction was not reported in the tamoxifen arm (n= 3094) of the above study; however, it has been reported in other trials or from other sources. The frequency has been calculated using the upper limit of the 95% confidence interval for the point estimate (based on 3/X, where X

represents the total sample size e.g. 3094). This is calculated as 3/3094 which equates to a frequency category of 'rare'.

[b] The event was not observed in other major clinical studies. The frequency has been calculated using the upper limit of the 95% confidence interval for the point estimate (based on 3/X, where X represents the total sample size of 13,357 patients in the major clinical studies). This is calculated as 3/13,357 which equates to a frequency category of 'very rare'.

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

[&] 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).

[%] Elevation of serum triglyceride levels, in some cases with pancreatitis, may be associated with the use of tamoxifen.

[$] Visual disturbance such as cataracts, retinopathy and corneal changes, mainly in patients treated with exceptionally high doses for a long period of time.

Side effects can be classified as either due to the pharmacological action of the drug, 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 therapeutic effect. Persistent side effects may necessitate the discontinuance of treatment.

Primary prevention of breast cancer risk

The most common adverse events reported from studies in women at increased risk of breast cancer, and occurring more frequently during treatment with Tamoxifen than with placebo, were those associated

specifically with the pharmacological action of Tamoxifen such as vasomotor symptoms (hot flushes, night sweats), menstrual abnormalities\irregularities, vaginal discharge, and vaginal dryness.
In the primary prevention trials Tamoxifen significantly increased the incidence of endometrial cancer, deep vein thrombosis, and pulmonary embolism compared with placebo, but the absolute increase in risk was small. The risk of developing cataracts was also significantly increased with Tamoxifen.

Women under 50 years old

A meta-analysis of risk reduction trials stratified by age showed that while women over 50 years old at randomisation had a significantly increased risk of endometrial cancer compared with placebo (RR 3.32, 95% CI 1.95-5.67; p<0.0001), women aged under 50 years did not have a significantly increased risk of pulmonary embolism compared with placebo (RR 1.16, 95% CI 0.55-2.43; p=0.60) and their risk of deep vein thrombosis was only significantly increased during the active treatment phase (RR 2.30, 95% CI 1.23-4.31; p=0,009) but not after treatment had ended.

Gynaecological conditions and procedures

In placebo controlled trials of the use of Tamoxifen for the primary reduction of breast cancer risk, benign gynaecological conditions and procedures were more commonly reported with Tamoxifen. The IBIS-1 trial found that in 3573 women taking Tamoxifen compared to 3566 women on placebo, the following gynaecological conditions and procedures were more common in women taking Tamoxifen: abnormal bleeding (842 v 678, p<00001); endometrial polyps (130 v 65, p<0,0001); ovarian cysts (101 v 42, p<00001); hysteroscopy (228 v 138, P<0,0001); pelvic ultrasound (209 v 132, p<00001); dilation and curettage (178 v 94, p<00001); hysterectomy (154 v 104, p=0002) and oophorectomy (103 v 67, p=0006).

4.9 Overdosage

Symptoms

An overdosage would be expected to cause enhancement of the anti-oestrogenic side effects.

Animal studies have demonstrated that extremely high dosage (greater than 100 times the recommended daily dose) may cause 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 an ECG.

Management

There is no specific antidote to overdosage and treatment should be carried out symptomatically.

5. Pharmacological properties

5.1 Pharmacodynamics Properties

Pharmacotherapeutic group: Hormone antagonists and related agents, anti-oestrogens,

ATC Code: L02BA01

Tamoxifen competitively inhibits estrogen binding to its receptor, which is critical for it's activity in breast cancer cells. Tamoxifen leads to a decrease in tumor growth factor α and insulin-like growth factor 1, and an increase in sex hormone binding globulin. The increase in sex hormon binding globulin limits the amount of freely available estradiol.These changes reduce levels of factors that stimulate tumor growth.

Tamoxifen has also been shown to induce apoptosis in estrogen receptor positive cells. This action is thought to be the result of inhibition of protein kinase C, which prevents DNA synthesis. Alternate theories for the apoptotic effect of tamoxifen comes from the approximately 3 fold increase in intracellular and mitochondrial calcium ion levels after administration or the induction of tumor growth factor β.

5.2 Pharmacokinetics Properties

Absorption and Distribution

Following a single oral dose of 20 mg tamoxifen, an average peak plasma concentration of 40 ng/mL (range 35 to 45 ng/mL) occurred approximately 5 hours after dosing. The decline in plasma concentrations of tamoxifen is biphasic with a terminal elimination half-life of about 5 to 7 days. The average peak plasma concentration of N-desmethyl tamoxifen is 15 ng/mL (range 10 to 20 ng/mL). Chronic administration of 10 mg tamoxifen given twice daily for 3 months to patients results in average steady-state plasma concentrations of 120 ng/mL (range 67 to 183 ng/mL) for tamoxifen and 336 ng/mL (range 148 to 654 ng/mL) for N-desmethyl tamoxifen. The average steady-state plasma concentrations

of tamoxifen and N-desmethyl tamoxifen after administration of 20 mg tamoxifen once daily for 3 months are 122 ng/mL (range 71 to 183 ng/mL) and 353 ng/mL (range 152 to 706 ng/mL), respectively. After initiation of therapy, steady-state concentrations for tamoxifen are achieved in about 4 weeks and steady-state concentrations for N-desmethyl tamoxifen are achieved in about 8 weeks, suggesting a half-life of approximately 14 days for this metabolite. In a steady-state, crossover study of 10 mg tamoxifen citrate tablets given twice a day vs. a 20 mg tamoxifen citrate tablet given once daily, the 20 mg tamoxifen citrate tablet was bioequivalent to the 10 mg tamoxifen citrate tablets.

Metabolism

Tamoxifen is extensively metabolized after oral administration. 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.

Excretion

Studies in women receiving 20 mg of 14C tamoxifen have shown that approximately 65% of the administered dose was excreted from the body over a period of 2 weeks with fecal excretion as the primary route of elimination. The drug is excreted mainly as polar conjugates, with unchanged drug and unconjugated metabolites accounting for less than 30% of the total fecal radioactivity.

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 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 drug on which extensive clinical experience has been obtained.

6. Pharmaceutical Particulars

6.1 List of Excipients

Name of Ingredients
Mannitol
Starch
Polacrilin Potassium (Doshion P544)
Croscarmellose Sodium
Povidone (P.V.P. K-30)
Purified Talc
Magnesium Stearate
Polacrilin Potassium (Doshion P544)
Colloidal silicon dioxide

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 months from the date of manufacturing, when retained in the original carton.

6.4 Special precautions for storage

No special precaution required for storage, retain in original cartons

6.5. Nature and contents of container

Printed Aluminium Foil (0.02 x 171 mm) as lidding foil

Orange PVDC (0.30 x 175 mm) as base foil.

6.6 Special precautions for disposal and other handling

No special precaution for disposal required.

7. How Supplied

Tamoxifen 20 mg: White to off white circular shaped flat, beveled edge uncoated tablets scored on one side and embossed “20” on other side, packed in blister of 10 tablets. Such 10 blister packs of 10 tablets placed in a printed laminated carton along with patient information leaflet.

Tamoxifen 10 mg: White coloured, circular, flat, beveled edge uncoated tablets having break line on one side, packed in blister of 10 tablets. Such 10 blister packs of 10 tablets placed in a printed laminated carton along with patient information leaflet.

8. Storage Condition

Store below 30°C. Protected from light & moisture.

9. MARKETING AUTHORISATION NUMBERS IN ETHIOPIA
08571/08798/NMR/2021

10. DATE OF FIRST AUTHORISATION IN ETHIOPIA
Apr 5, 2023

11.DATE OF REVISION OF THE TEXT
09/2019