SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tamoxifen Teva 20mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tamoxifen Citrate 30.4 mg (equivalent to 20 mg tamoxifen).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round biconvex film coated tablet, scored on one side with the number "20" embossed above the score line and the letter "T" below it and plain on and the other side.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tamoxifen Teva is indicated for the palliative treatment of breast cancer generally in postmenopausal women, either alone or in combination with other modalities.

4.2 Posology and method of administration

Posology

Adults

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.

Elderly people

Similar dosing regimens of Tamoxifen Teva have been used in the eldery with breast cancer and in some of these patients it has been used as sole therapy.

Method of administration

For administration by the oral route.

4.3 Contraindications

Tamoxifen Teva should not be used in the following:

- Pregnancy. Premenopausal patients must be carefully examined before treatment to exclude the possibility of pregnancy (see also section 4.6).
- Hypersensitivity to the active substance or to any of the excipients listed in

section 6.1.

- Concurrent anastrozole therapy (see section 4.5).

4.4 Special warnings and precautions for use

Menstruation is suppressed in a proportion of premenopausal women receiving Tamoxifen Teva 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 Teva 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 Teva who report abnormal gynaecological symptoms, especially non-menstrual vaginal bleeding, or who presents with menstrual irregularities, vaginal discharge and symptoms such as pelvic pain or pressure should be promptly investigated.

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

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.

<u>Venous thromboembolism</u>

- A 2-3-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 (cross-reference 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 before treatment with tamoxifen. This risk is also increased by concomitant chemotherapy (see section 4.5). Long-term anticoagulant prophylaxis may be justified for some patients 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, 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 Teva 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 sections 4.5 and 5.2).

Radiation recall has been reported very rarely in patients on tamoxifen who have received prior radiotherapy. The reaction 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.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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. 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.

4.5 Interaction with other medicinal products and other forms of interaction

When Tamoxifen Teva is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur. Where such co-administration is initiated, careful monitoring of the patient is recommended.

When Tamoxifen Teva is used in combination with cytotoxic agents for the treatment of breast cancer, 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 Teva 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 reduction in plasma level of an active tamoxifen metabolite, 4-hydroxy-N- desmethyltamoxifen (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 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 (see sections 4.4 and 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women should be advised not to become pregnant whilst taking Tamoxifen Teva 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 Teva or within nine months of cessation of therapy.

Pregnancy
Tamoxifen Teva must not be administered during 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 estradiol, ethinylestradiol, 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. 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.

Breast-feeding
Limited data suggest that Tamoxifen Teva and its active metabolites are excreted and

accumulate over time in human milk, therefore the drug is not recommended during breast-feeding. The decision either to discontinue nursing or discontinue Tamoxifen Teva should take into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Tamoxifen Teva 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

The following definitions apply to the incidence of undesirable effects: Frequencies are defined as: 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), not known (cannot be estimated from the available data).

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.

Table 1 Adverse Drug Reactions (ADR) by System Organ Class (SOC) and Frequency.

SOC	Frequency	Adverse Drug Reaction
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Uterine fibroids
	Uncommon	Endometrial cancer
	Rare	Uterine Sarcoma (mostly malignant mixed Mullerian tumours)[1] Tumour Flare[1]
Blood and lymphatic system disorders	Common	Anaemia
	Uncommon	Thrombocytopenia Leukopenia
	Rare	Neutropenia Agranulocytosis
Immune system disorders	Common	Hypersensitivity reactions
Metabolism and nutrition disorders	Very common	Fluid retention
	Uncommon	Hypercalcaemia (in patients with bony metastases)
Nervous system disorders	Common	Ischaemic cerebrovascular events Headache Light headedness Sensory disturbances (including paraesthesia and dysgeusia)

	Rare	Optic neuritis
Eye disorders	Common	Cataracts Retinopathy
	Uncommon	Visual disturbances
	Rare	Corneal changes Optic neuropathy[1]
Vascular disorders	Very Common	Hot flushes
	Common	Thromboembolic events (including deep vein thrombosis, microvascular thrombosis and pulmonary embolism)
Respiratory, thoracic and mediastinal disorders	Uncommon	Interstitial pneumonitis
Gastrointestinal disorders	Very common	Nausea
	Common	Vomiting Diarrhoea Constipation
	Uncommon	Pancreatitis
Hepatobiliary disorders	Common	Changes in liver enzymes Fatty liver
	Uncommon	Cirrhosis of the liver
	Rare	Hepatitis Cholestasis[1] Hepatic failure[1] Hepatocellular injury[1] Hepatic necrosis[1]
Skin and subcutaneous tissue disorders	Very common	Skin Rash
	Common	Alopecia
	Rare	Angioedema Steven-Johnsons syndrome[1] Cutaneous vasculitis[1] Bullous pemphigoid[1] Erythema multiforme[1] Toxic epidermal necrolysis[1]
	Very rare	Cutaneous lupus erythematosus[2]
	Not known	Exacerbation of hereditary angioedema
Musculoskeletal and connective tissue disorders	Common	Leg cramp Myalgia
Reproductive system and breast disorders	Very common	Vaginal bleeding Vaginal discharge

	Common	Pruritus valvae Endometrial changes (including hyperplasia and polyps)
	Rare	Endometriosis[1] Cystic ovarian swelling[1] Vaginal polyps
Congenital, familial and genetic disorders	Very rare	Porphyria cutanea tarda[2]
General disorders and administration site conditions	Very common	Fatigue
Investigations	Common	Elevated triglycerides
Injury, poisoning and procedural complications	Very rare	Radiation Recall[2]
Psychiatric Disorders	Very common	Depression

[1] This adverse drug reaction was <u>not</u> 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'.

[2] 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'.

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 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, toxic epidermal necrolysis, cutaneous vasculitis, and bullous pemphigoid) and commonly hypersensitivity reactions including angioedema have been reported.

Cases of exacerbation of angioedema have been reported in patients with hereditary angioedema receiving tamoxifen.

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 Teva 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.

Depression has been reported with frequency very common in association

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.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

On theoretical grounds, an overdosage would be expected to cause enhancement of the pharmacological side effects mentioned above. Observations in animals show that extreme overdosage (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 to overdosage, and treatment must be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-estrogens. ATC code: L02BA01**.**

Tamoxifen is a non-steroidal, triphenylethylene-based drug 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 (see sections 4.4, 4.5 and 5.2)

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.

The available studies have mainly been performed in postmenopausal women (see sections 4.4 and 5.2).

5.2 Pharmacokinetic properties

After oral administration, tamoxifen is absorbed rapidly with maximum serum concentrations attained within 4-7 hours. Steady state concentrations (about 300ng/ml) are achieved after four weeks treatment with 40mg daily. The drug is highly protein bound to serum albumin (>99%). 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. Excretion occurs primarily via the faeces and an elimination half-life of approximately seven days has been calculated for the drug itself, whereas that for N- desmethyltamoxifen, the principal circulating metabolite, is 14 days.
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.

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. Relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, Sodium Starch Glycolate, Povidone, Hypromelose, Magnesium Stearate, Colloidal Silicon Dioxide, Titanium Dioxide, Polyethylene glycol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store this medicine in a dry place, under 25°C.
Protect from light.

6.5 Nature and contents of container

The product is supplied in blisters packed in carton box of 10, 30, 100 or 250 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 LICENCE HOLDER AND MANUFACTURER

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8 REGISTRATION NUMBER

142.98.33084

The leaflet was revised in January 2022 according to MOHs guidelines