Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tamoxifen 20 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains tamoxifen citrate equivalent to 20 mg of tamoxifen.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Tamoxifen 20mg Tablet:
White, round, biconvex tablet debossed with 'TN' above the score and '20' below the score on one side of the tablet and 'G' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tamoxifen is indicated in the treatment of breast cancer**.**

4.2 Posology and method of administration

Posology

Breast cancer: Adults (including the elderly): The dosage range is 20 to 40 mg daily, given either in divided doses twice daily or as a single dose once daily.
In early disease, it is currently recommended that treatment is given for not less than 5 years. The optimal duration of tamoxifen therapy remains to be determined.

Paediatric population: The use of tamoxifen is not recommended in children, as safety and efficacy have not been established (see sections 5.1 and 5.2).

Method of administration
For administration by the oral route.

4.3 Contraindications

Tamoxifen should not be used in the following:

- 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 (see also section 4.6).
- hypersensitivity to the active substance, or to any of the excipients listed in section 6.1.

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.

A small number of cases of endometrial hyperplasia, endometrial polyps andan increased incidence of endometrial cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours) have been reported in association with tamoxifen treatment. The underlying mechanism is unknown, but may be related to the oestrogen-like effects of tamoxifen.

Any patients receiving or having previously received tamoxifen, who report abnormal gynaecological symptoms, especially vaginal bleeding, including should be promptly investigated.

Nonetheless, the possibility that Tamoxifen may affect the development of endometrial pathology, including neoplasia, should be kept in mind when designing treatment regimes.

Investigations in different in vivo and in vitro systems have shown that tamoxifen has a genotoxic potential following hepatic activation. Gonadal tumours in mice and liver tumours in rats receiving tamoxifen have been reported in long-term studies. The clinical relevance of these findings has not been established.

A number of second primary tumours, occurring at sites other than the endometrium and the opposite breast, have been reported in clinical trials, following treatment of breast cancer patients with tamoxifen. No casual links have been established and the clinical significance of these observations remains unclear.

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

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

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.

In an uncontrolled trial in 28 girls aged 2–10 years with McCune Albright Syndrome (MAS), who received 20 mg tamoxifen once a day for up to 12 month's duration, mean uterine volume increased after 6 months of treatment and doubled at the end of the one-year study. While this finding is in line with the pharmacodynamic properties of tamoxifen, a causal relationship has not been established (see section 5.1).

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).

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

Venous thromboembolism
A 2-3-fold increase in the risk for VTE has been demonstrated in healthy tamoxifen-treated women (see section 4.8).
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 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 (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 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 anti-coagulant treatment.

If any patients with VTE, tamoxifen should be stopped immediately and appropriate anti-thrombosis measures initiated. Tamoxifen should not be restarted unless there is a compelling alternative explanation for their

thrombotic event. In patients receiving tamoxifen for breast cancer, 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

When Tamoxifen is used in combination with cytotoxic agents, there is increased risk of thromboembolic event occurring (see also section 4.8).

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

The known principal pathway for tamoxifen metabolism in humans is demethylation, catalysed by CYP3A4 enzymes. Pharmacokinetic interaction with the CYP3A4 inducing agent rifampicin, showing a reduction in tamoxifen plasma levels has been reported in the literature. The relevance of this finding is not known.

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

Pregnancy
Tamoxifen 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 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. 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 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 appraised of the potential risks to the foetus, should they become pregnant whilst taking tamoxifen; or within nine months of cessation of therapy.

Breast-feeding
Limited data suggest that tamoxifen and its active metabolites are excreted and accumulate over time in human milk and therefore, the drug is not recommended during breast-feeding. 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 machines

Tamoxifen is unlikely to impair the ability of patients to drive or use machinery. However, fatigue has been reported with the use of tamoxifen and caution should be observed when driving or operating 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.

Adverse drug reactions (ADRs) can be classified as either due to the pharmacological action of the drug e.g. hot flushes, vaginal bleeding, vaginal discharge and pruritus vulvae, or as more general ADRs e.g. nausea, fluid retention and skin rash. When such side effects are severe, it may be possible to control them by simple reduction of dosage (within the recommended dose range) without loss of control of the disease.

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)[a] Tumour flare[a]
Blood and lymphatic system disorders	Common	Anaemia
	Uncommon	Thrombocytopenia Leukopenia
	Rare	Neutropenia[a] Agranulocytosis[a]
Immune system disorders	Common	Hypersensitivity reactions
Metabolism and nutrition disorders	Very common	Fluid retention
	Uncommon	Hypercalcaemia (in patients with bone 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 disturbance
	Rare	Corneal changes Optic neuropathy[a]
Vascular disorders	Very common	Hot flushes
Multiple SOC Terms	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	Cholestasis[a] Hepatitis Hepatic failure[a] Hepatocellular injury[a] Hepatic necrosis[a]
Skin and subcutaneous tissue disorders	Very common	Skin rash
	Common	Alopecia
	Rare	Angioedema Stevens-Johnson syndrome[a] Cutaneous vasculitis[a] Bullous pemphigoid[a] Erythema multiforme[a]
	Rare	Toxic epidermal necrolysis
	Not Known	Exacerbation of hereditary angioedema
	Very Rare	Cutaneous lupus erythematosus[b]
Musculoskeletal and connective tissue disorders	Common	Leg cramp Myalgia
Reproductive system and breast disorders	Very common	Vaginal bleeding Vaginal discharge
	Common	Pruritus vulvae Endometrial changes (including hyperplasia and polyps)
	Rare	Endometriosis[a] Cystic ovarian swelling[a] Vaginal polyps
Congenital, familial and genetic disorders	Very rare	Porphyria cutanea tarda[b]
General disorders and administration site conditions	Very common	Fatigue
Investigations	Common	Elevated triglycerides
Injury, poisoning and procedural complications	Very rare	Radiation Recall[b]

[a] 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'.

[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.

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

When Tamoxifen is used in combination with cytotoxic agents, there is increased risk of thromboembolic events occurring.

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 via HPRA Pharmacovigilance.Website: www.hpra.ie.

4.9 Overdose

On theoretical grounds, overdosage would be expected to cause enhancement of the anti-oestrogenic 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: Hormone antagonists and related agents, anti-oestrogens, ATC Code: L02BA01

Mechanism of action
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 women with oestrogen receptor positive/unknown breast tumours, adjuvant tamoxifen has been shown to significantly reduce recurrence of the disease and improve 10-year survival, achieving a significantly greater effect with five years treatment than with 1 or 2 years treatment. These benefits appear to be largely irrespective of age, menopausal status, tamoxifen dose and additional chemotherapy.

In the clinical situation, it's recognised that tamoxifen leads to reduction in levels of blood total cholesterol and low density lipoproteins in post-menopausal women of the order 10-20%. Additionally, tamoxifen has been reported to lead to maintenance of bone mineral density in postmenopausal women.

Paediatric population
An uncontrolled trial was undertaken in a heterogeneous group of 28 girls aged 2 to 10 years with McCune Albright Syndrome (MAS), who received 20 mg tamoxifen once a day for up to 12 months duration.

Among the patients who reported vaginal bleeding during the pre-study period, 62% (13 out of 21 patients) reported no bleeding for a 6 month period and 33% (7 out of 21 patients) reported no vaginal bleeding for the duration of the trial. Mean uterine volume increased after 6 months of treatment and doubled at the end of the one-year study.

While this finding is in line with the pharmacodynamic properties of tamoxifen, a causal relationship has not been established (see section 4.4). There are no long-term safety data in children. In particular, the long term effects of tamoxifen on growth, puberty, and general development have not been studied.

CYP2D6 polymorphism
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

Absorption
After oral administration, tamoxifen is absorbed rapidly with maximum serum concentrations attained within 4-7 hours. Steady state concentrations (about 300 ng/ml) are achieved after four weeks treatment with 40 mg daily.

Distribution
The drug 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.

Elimination
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.

Special patient populations

Paediatric population
In a clinical study where girls between 2 and 10 years with McCune Albright Syndrome (MAS) received 20 mg tamoxifen once a day for up to 12 months duration, there was an age-dependent decrease in clearance and an increase in exposure (AUC), (with values up to 50% higher in the youngest patients) compared with adults.

CYP2D6 polymorphism
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

Investigations in different in-vivo and in-vitro systems have shown that tamoxifen has a genotoxic potential following hepatic activation. 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 that on which extensive clinical experience has been obtained. Relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics (see section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)

Maize Starch
Croscarmellose Sodium
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25ºC.

Blisters:
Store in the original package in order to protect from light and moisture.

Bottles:
Keep the container tightly closed in order to protect from light and moisture.

6.5 Nature and contents of container

Polyvinylchloride (PVC)/aluminium foil blister packs containing 30, 50 or 100 tablets.
Or
Polypropylene tablet container with polyethylene tamper evident caps, containing 30, 50 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Viatris Limited
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Mulhuddart
Dublin 15
Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23266/052/001

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