Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tamox 10 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg tamoxifen (as tamoxifen citrate)
Excipients with known effect: Also contains 72.2mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White, round, biconvex tablets, diameter: 7.0 – 7.3 mm, height: 2.9 – 3.3 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tamox is indicated in the treatment of breast cancer.

4.2 Posology and method of administration

Method of Administration:
Oral.

Recommended Dosage Schedule:
Breast Cancer: Adults (including elderly): The dose range is 20 to 40 mg daily, given either as a single dose once daily or in divided doses twice 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 Tamox is not recommended in children, as safety and efficacy have not been established. (See section 5.1 and 5.2)

4.3 Contraindications

Tamox 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. An increased incidence of endometrial 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.

Any patients receiving or having previously received tamoxifen, who report abnormal gynaecological symptoms, especially vaginal bleeding, 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 regimens.

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 secondary primary tumours, occurring at sites other than the endometrium and the opposite breast, have been reported in clinical trials, following the treatment or breast cancer patients with tamoxifen. No causal link has been established and the clinical significance of these observations remains unclear.

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

When starting tamoxifen therapy the patient should undergo an ophthalmological examination. If visual changes occur while on tamoxifen therapy it is urgent that the ophthalmological investigation be performed, because some of such changes may resolve after cessation of treatment if recognised at an early stage.

In cases of severe thrombocytopenia, leucocytopenia or hypercalcaemia, individual risk-benefit assessment and thorough medical supervision are necessary.
The blood count including thrombocytes, liver function test and serum calcium should be controlled regularly.

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

Children: In an uncontrolled trial in 28 girls aged 2 - 10 years with McCune Albright Syndrome (MAS), who received 20mg once a day for up to 12 months 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).

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.

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

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

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).

4.5 Interaction with other medicinal products and other forms of interaction

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

When Tamoxifen is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effects may occur. Where such co-administration is initiated, careful monitoring of the patient is recommended.
In order to avoid bleeding during a possible thrombocytopenic interval thrombocyte aggregation inhibitors should not be combined with tamoxifen.

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

The use of tamoxifen in combination with an aromatase inhibitor 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 tamxifen plasma levels have been reported in the literature. The relevance of this finding is not known.

Pharmacokinetic interaction with CYP2D 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 section 4.4 and 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy: TAMOX 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 1,000 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 of childbearing age/Contraception in men and women
Due to the genotoxic potential of Tamoxifen (see section 5.3), women of childbearing potential should use effective contraceptive measures while being treated with Tamoxifen and for 9 months following completion of treatment.
Men are recommended to use effective contraceptive measures and to not father a child while receiving Tamoxifen and for 6 months following completion of treatment.

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 Tamox should take into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Tamox is unlikely to impair the ability of patients to drive or operate machinery. However, visual disturbances and light-headedness have been observed commonly and fatigue have been reported with the use of tamoxifen. Caution should be observed when driving or using machinery while such symptoms persist.

4.8 Undesirable effects

The following convention has been utilised for the classification of frequency: 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 (ADR's) 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 ADR's e.g. nausea, fluid retention and skin rash. When such side effects are severe, it may be possible to control them by a simple reduction of dosage (within the recommended dose range) without loss of control of the disease.

Blood and lymphatic system disorders
Common: anaemia
Uncommon: leukopenia, thrombocytopenia
Rare: agranulocytosis[a], neutropenia[a]
Very rare: severe neutropenia, pancytopenia

Metabolism and nutrition disorders
Very common: fluid retention
Common: increase in serum triglycerides
Uncommon: hypercalcaemia (in patients with bony metastases)
Very rare: severe hypertriglyceridaemia partially with pancreatitis

Nervous system disorders
Common: light-headedness, headache, ischaemic cerebrovascular events, sensory disturbances, including paraesthesia and dysgeusia.
Rare: optic neuritis

Eye disorders
Common: cataracts, retinopathy
Uncommon: visual disturbances.
Rare: optic neuropathya, corneal changes

Vascular disorders
Very common: hot flushes
Common: ischaemic cerebrovascular events, leg cramps
Uncommon: stroke

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 enzyme levels, fatty liver
Uncommon: cirrhosis of the liver
Rare: hepatitis, cholestasis[a], hepatic failure[a], hepatocellular injury[a], hepatic necrosis[a].

Skin and subcutaneous tissue disorders
Very common: skin rash
Common: alopecia
Rare: angioedema, steven-johnsons syndrome[a], cutaneous vasculitis[a], bullous pemphigoid[a], erythema multiforme[a]. toxic epidermal necrolysis[a]
Very rare: cutaneous lupus erythematosus[b]
*Not known:*Exacerbation of hereditary angioedema.

Musculoskeletal and connective tissue disorders
Common: myalgia, leg cramp

Reproductive system and breast disorders
Very common: vaginal discharge, vaginal bleeding
Common: pruritus vulvae, endometrial changes (including hyperplasia and polyps)

Uncommon: endometrial cancer
Rare: cystic ovarian swelling[a], endometriosis[a], vaginal polyps

Immune System Disorders:
Common: hypersensitivity reactions.

Investigations:
Common: elevated triglycerides

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]

Congenital, familial and genetic disorders
Very rare: porphyria cutanea tarda[b]

General disorders and administration site conditions
Very common: fatigue

Multiple SOC Terms
Common: Thromboembolic events (including deep vein thrombosis, microvascular thrombosis and pulmonary embolism.

Injury, poisoning and procedural complications
Very rare: Radiation Recall[b]

[a] This adverse 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 if 13,357 patients in the major clinical studies). This is calculated as 3/13,357 which equates to a frequency category of 'very rare'.

Skin rashes (including rare reports of erythem a 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. Falls in platelet count, usually only to 80,000-90,000 per cu mm but occasionally lower have been reported in patients taking tamoxifen for breast cancer.

Cases of visual disturbance including rare reports of corneal changes and common reports of retinopathy have been described in patients receiving tamoxifen therapy. Cataracts has 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.

Uterine fibroids and other endometrial changes including hyperplasia and polyps have been reported commonly with the use of tamoxifen.

Cystic ovarian swellings have rarely been observed in women receiving tamoxifen. 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 rarely cases of agranulocytosis have been reported.

There is evidence of ischaemic cerebrovascular events and thromboembolic events, including deep vein thrombosis, microvascular thrombosis and pulmonaryembolism, occurring commonly during Tamoxifen therapy. When Tamoxifen is used in combination with cytotoxic agents there is 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, cholestatis 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.

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

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

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

Vaginal polyps have rarely been observed in women 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.

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 x 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

ATC code: L02BA01

Pharmacotherapeutic group: anti-estrogens

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 5 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 is recognised that tamoxifen leads to reduction in levels of blood total cholesterol and low-density lipoproteins in postmenopausal women of the order of 10-20%. Additionally tamoxifen has been reported to lead to maintenance of bone mineral density in postmenopausal women.

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 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) reported no vaginal bleeding for the duration of the trial. Mean uterine volume increased after 6 pharmacodynamic properties of tamoxifen, a casual 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 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 300 ng/ml) are achieved after four weeks treatment with 40 mg 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 similar pharmacological profile to the parent compound and thus contribute to the therapeutic effect.

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.

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.

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.

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 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

Lactose monohydrate
Povidone (Kollidon 25)
Sodium starch glycolate (Type A)
Microcrystalline cellulose
Magnesium stearate

Tablet Coating:

Opadry White consisting of:
Hypromellose
Lactose monohydrate
Macrogol 4000
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

Tamox 10 mg Tablets are blister packed in PVC/aluminium strips of 10 tablets. The blisters are further packed in outer cardboard-lithographed boxes and are available in sales boxes of 10 and 30 tablets each.

Not all packs sizes may be marketed.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/022/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 February 1992

Date of last renewal: 25 February 2007

10 DATE OF REVISION OF THE TEXT

February 2026