Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tamoxifen Rosemont 10 mg/5 ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml dose of oral solution contains tamoxifen 10mg (as tamoxifen citrate)

Excipients with known effect:
Ethanol - 750mg per 5ml
Sorbitol solution (non-crystallising) (E420) - 1g per 5ml
Glycerol (E422) – 2.25g per 5 ml
Propylene glycol (E1520) – 503.35mg per 5ml

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution

A clear colourless liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Adjuvant treatment of oestrogen-receptor positive early breast cancer
- Treatment of oestrogen-receptor positive locally advanced or metastatic breast cancer

4.2 Posology and method of administration

Posology
Adjuvant treatment of breast cancer, Adults (including elderly):
The recommended dose is 20mg, given either in divided doses twice daily or as a single dose once daily. The current recommended treatment duration is five years; however the optimum duration has not been established.

Treatment of locally advanced or metastatic breast cancer:
The recommended dose is 20mg to 40mg, given either in divided doses twice daily or as a single dose once daily.

Paediatric Population
Children: Not applicable.

Method of Administration
For oral use.

4.3 Contraindications

Pregnancy and lactation
Hypersensitivity to tamoxifen 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

Premenopausal patients must be carefully examined before treatment to exclude pregnancy.
Women should be informedof the potential risks to the foetus, should they become pregnant whilst taking tamoxifen; or within two months of cessation of therapy.

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

Menstruation is suppressed in a proportion of premenopausal women receiving tamoxifen for the treatment of breast cancer.

Any patients who have received tamoxifen therapy and have reported abnormal vaginal bleeding or patients presenting with menstrual irregularities, vaginal discharge and pelvic pressure or pain should undergo prompt investigationdue to the increased incidence of endometrial changes including hyperplasia, polyps, cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours)which has been reported in association with tamoxifen treatment. The underlying mechanism is unknown, but may be related to the oestrogenic-like effect of tamoxifen.

Before initiating tamoxifen a complete personal history should be taken. Physical examination (including pelvic examination) should be guided by the patients past medical history and by the 'contraindications' and 'special warnings and precautions for use' warnings for use for tamoxifen. During treatment periodic check-ups including gynaecological examination focussing on endometrial changes are recommended of a frequency and nature adapted to the individual woman and modified according to her clinical needs.

When starting tamoxifen therapy the patient should undergo an ophthalmological examination. If visual changes (cataracts and retinopathy) occur while on tamoxifen therapy it is urgent that an 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.

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 (see section 4.5).

•VTE risk is further increased by severe obesity, increasing age, concomitant chemotherapy and all other risk factors for VTE (see section 4.5). The risks and benefits should be carefully considered for all patients before treatment with tamoxifen. Long-term anti-coagulant prophylaxis may be justified for some patients with breast cancer who have multiple risk factors for VTE.

• Surgery and immobility: Tamoxifen treatment should only be stopped if the risk of tamoxifen-induced thrombosis clearly outweighs the risks associated with interrupting treatment. All patients should receive appropriate thrombosis prophylactic measures and should include graduated compression stockings for the period of hospitalisation, early ambulation, if possible, and anticoagulant treatment.

• Patients should be advised to seek immediate medical attention if they become aware of any symptoms of VTE; in such cases, tamoxifen therapy should be stopped and appropriate anti-thrombosis measures initiated.

• In the above cases, the risks and benefits to the patient of tamoxifen therapy must be carefully considered. In selected patients with breast cancer, the continued use of tamoxifen with prophylactic anticoagulation may be justified.

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

In an uncontrolled trial in 28 girls aged 2–10 years with McCune Albright Syndrome (MAS), who received 20 mg 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).

The blood count including thrombocytes, liver function test and serum calcium should be controlled regularly.

Assessment of triglycerides in serum may be advisable because in most published cases of severe hypertriglyceridemia dyslipoproteinemia was the underlying disorder.

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 (CYPD2D6 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).

Clinical trial data shows an increase in the incidence of depression in patients with breast cancer treated with tamoxifen. It is not clear whether this is related to tamoxifen treatment or to other factors (cancer diagnosis, surgery, chemotherapy, radiotherapy etc.). Clinicians supervising tamoxifen treatment should be aware of this increased incidence and screen patients for depression.

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.

Paediatric Population
Tamoxifen is not intended for use in children.

Excipient Warnings

- This product contains 19%v/v ethanol, i.e. 750mg per dose equivalent to 19ml of beer or 8ml of wine per dose. A dose of 20ml of this medicine administered to an adult weighing 70 kg would result in exposure to 43mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 7mg/100 ml. Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects, in particular in young children with low or immature metabolic capacity.
- This medicine contains 1g sorbitol (E420) in each 5ml. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.
- This product contains glycerol (E422) which may cause headache, stomach upset and diarrhoea.
- This medicine contains 503.35mg propylene glycol in each 5ml.

4.5 Interaction with other medicinal products and other forms of interactions

Coumarin-type anti-coagulants:
When used in combination with tamoxifen solution a significant increase in anticoagulant effect may occur. In the case of concomitant treatment particularly during the initial phase thorough monitoring of the coagulation status is mandatory.

Thrombocyte aggregation inhibitors:
In order to avoid bleeding during a possible thrombocytopenic interval thrombocyte aggregation inhibitors should not be combined with tamoxifen.

Cytotoxic agents:
When used in combination with tamoxifen solution 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. Tamoxifen and its metabolites have been found to be inhibitors of hepatic

cytochrome p-450 mixed function oxidases. The effect of tamoxifen on metabolism and excretion of other antineoplastic drugs, such as cyclophosphamide and other drugs that require mixed function oxidases of activation, is not known.

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

Bromocriptine:
Tamoxifen increases the dopaminergic effect of bromocriptine.

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

As tamoxifen is metabolised by cytochrome P450 34A, care is required when co-administered with drugs known to induce this enzyme, such as rifampicin, as tamoxifen levels may be reduced. The clinical relevance of this reduction is unknown.

Plasma concentrations of tamoxifen may be increased by concomitant treatment with CYP3A4 inhibitors.

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. The relevance of this to clinical practice 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 section 4.4 and 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy:
There are only data from a small number of women who have been exposed to tamoxifen during pregnancy. Although no causal relationship has been established, only a small number of spontaneous abortions, birth defects and foetal deaths in women treated with tamoxifen during pregnancy have been reported.
Animal studies have shown reproduction toxicity (see section 5.3). Although the clinical relevance of the observed preclinical effects 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. Such exposure has not been reported to cause subsequent vaginal adenosis or clear cell carcinoma of the vagina or cervix in the small number of young women known to have been exposed in utero to tamoxifen.
Since the use of tamoxifen during pregnancy is contraindicated, women should be advised not to become pregnant whilst taking tamoxifen and within two months after stopping tamoxifen medication and should use barrier or other non hormonal contraceptive methods if sexually active.
Breast-feeding:
It is not known whether tamoxifen is excreted into breast milk. Therefore, tamoxifen treatment is contraindicated during breast-feeding. Tamoxifen inhibits lactation in humans and no rebound lactation was observed after completion of therapy.

4.7 Effects on ability to drive and use machines

No studies on the effects of the ability to drive and use machines have been performed.

Since fatigue, visual disturbances and light-headedness have been observed commonly with the use of tamoxifen, caution is advised when driving or using machines. The amount of alcohol in this product may impair the ability to drive or use machines.

4.8 Undesirable effects

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 frequencies of adverse events are ranked according to the following: 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).

Neoplasms benign, malignant and unspecified
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: Temporary thrombocytopenia (usually 80,00-90,000 per cu mm but occasionally lower), leukopenia (see sections 4.4 and 4.5)
Rare: Temporary reductions in blood count such as neutropenia[a] (sometimes severe), agranulocytosis[a]
Very Rare: Pancytopenia

Immune system disorders
Common: Hypersensitivity reactions

Metabolism and nutrition disorders
Very common: Fluid retention
Uncommon: Hypercalcaemia (in patients with bony metastases) on initiation of therapy (see section 4.4)
Very rare: Severe hypertriglyceridemia which may be partly combined with pancreatitis

Psychiatric disorders
Very Common:Depression (it is not known whether this is related to tamoxifen treatment or to other factors but depression is very common in women with breast cancer, see section 4.4)

Nervous system disorders
Common: Light-headedness, headache, cerebral ischaemic events, sensory disturbances (including paraestheia and dysgeusia)
Rare: Optic neuritis

Eye disorders
Common: Cataracts and /or retinopathy that are only partly reversible. The risk for cataracts increases with the duration of tamoxifen treatment
Uncommon: Visual disturbances
Rare: Corneal changes. Optic neuropathy[a] that is only partly reversible. In a small number of cases, blindness has occurred.

Vascular disorders
Very common: Hot flushes
Common: Thromboembolic events, including deep vein thrombosis, microvascular thrombosis and pulmonary embolism. The risk increases when tamoxifen is used in combination with cytotoxic agents (see sections 4.4 and 4.5)

Respiratory, thoracic and mediastinal disorders
Uncommon: Interstitial pneumonitis

Gastrointestinal disorders
Very common: Nausea
Common: Vomiting, diarrhoea and constipation
Uncommon: Pancreatitis

Hepatobiliary disorders
Common: Changes in liver enzyme levels, fatty liver
Uncommon: Cirrhosis of the liver
Rare: Hepatitis and cholestasis[a], hepatic failure[a], hepatocellular injury[a] and hepatic necrosis[a]. Some cases of more severe liver abnormalities have proved fatal

Skin and subcutaneous tissue disorders
Very common: Skin rash
Common: Alopecia
Rare: Angioedema, Stevens-Johnson-syndrome[a], cutaneous vasculitis[a], bullous pemphigoid[a] or erythema multiforme[a]
Very rare: Cutaneous lupus erythematosus[b]

Musculoskeletal and connective tissue disorders
Common: Leg cramp, myalgia

Reproductive system and breast disorders
Very common: Vaginal discharge, vaginal bleeding
Common: Pruritus vulvae, endometrial changes (including hyperplasia and polyps)
Rare: Suppression of menstruation, cystic ovarian swellings[a], endometriosis and vaginal polyps

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

General disorders and administration site conditions
Very common: Fatigue
Common: Bone and tumour pain

Investigations
Common: Elevated triglycerides, in some cases with pancreatitis

Injury, poisoning and procedural complications
Very rare: 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 sing 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'.
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 undesirable events are severe it may be possible to control them by a simple reduction of dosage without loss of control of the disease. If undesirable events do not respond to this measure, it may be necessary to cease 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. Healthcare professional are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, e-mail: medsafety@hpra.ie.

4.9 Overdose

At doses of 160mg/m^2 daily and higher, changes in ECG (QT-prolongation) and at doses of 300 mg/m^2 daily, neurotoxicity (tremor, hyperreflexia, gait disorders, and dizziness) occurred.

Overdosage of tamoxifen will increase the anti-oestrogenic effects. There is no specific antidote to overdosage and treatment should therefore be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hormone antagonists and related agents
ATC Code: L02B A01

Tamoxifen is a non-steroidal anti-oestrogen and inhibits the effects of endogenous oestrogen, probably by binding with oestrogen receptors. Tamoxifen competes for the binding sites with estradiol and by occupying the receptor reduces the amount of receptor available for endogenous estradiol. Tamoxifen also prevents the normal feedback inhibition of oestrogen synthesis in the hypothalamus and in the pituitary.

Tamoxifen decreases cell division in oestrogen-dependent tissues. In metastatic breast cancer, partial or complete remissions were observed in 50-60% of cases, particularly in bone and soft tissue metastases if oestrogen-receptors were found in the tumour. In cases of negative hormone-receptor status, particularly of the metastases only approx. 10% showed objective remissions. Women with oestrogen receptor- positive tumours or tumours with unknown receptor status who received adjuvant treatment with tamoxifen experienced significantly less tumour recurrences and had a higher 10-year survival rate. The effect was greater after 5 years of adjuvant treatment compared with 1-2 years of treatment. The benefit appears to be independent of age, menopausal status, daily tamoxifen dose and additional chemotherapy.

In postmenopausal women, tamoxifen has no effect on the plasma concentrations of oestrogens but reduces the concentrations of LH-, FSH-, and prolactin, however within the normal range. Additionally tamoxifen has been reported to lead to maintenance of bone mineral density in postmenopausal women.

In premenopausal women, tamoxifen can increase the concentrations of oestrogens and prostagens but they will return to predose levels after discontinuation of the treatment.

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%. Tamoxifen increases steroid- and thyroxine-binding proteins and can thus affect the concentrations of cortisol and thyroid hormones. Additionally, tamoxifen reduces the plasma concentrations of antithrombin III

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 well-absorbed achieving maximum serum concentrations within 4 - 7 hours and is extensively metabolised.

Distribution:
Tamoxifen concentrations have been observed in lung, liver, adrenals, kidney, pancreas, uterus and mammary tissues.

Metabolism:
Tamoxifen 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. After four weeks of daily therapy, it was observed that steady state serum levels were achieved and an elimination half-life of seven days was calculated whereas that for N-desmethyltamoxifen, the principal circulating metabolite, is 14 days.

Excretion:
Elimination occurs, chiefly as conjugates with practically no unchanged drug, principally through the faeces and to a lesser extent through the kidneys.

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

Although reproductive toxicology studies in rats, rabbits and monkeys have shown no teratogenic potential, tamoxifen was associated in rodent models of foetal reproductive tract development with changes similar to those caused by estradiol, ethynylestradiol, clomifene and diethylstilbestrol (DES). The clinical relevance of these changes is unknown. However some of them, especially vaginal adenosis, are similar to those seen in young women who were exposed to DES in utero (see section 4.6).

Tamoxifen was not mutagenic in a range if in vitro and in vivo mutagenicity tests. 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol
Glycerol (E422)
Propylene glycol (E1520)
Sorbitol solution (non-crystallising) (E420)
Natural aniseed flavouring A05 (flavouring preparations, isopropyl alcohol, water)
Liquorice flavouring L03 (flavouring preparations, natural flavouring substances, artificial flavouring substances, propylene glycol (E1520), isopropyl alcohol)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the medicinal product as packaged for sale: 2 years
Shelf life after first opening the container: 3 months

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Bottle: Amber (Type III) glass
Closure: HDPE, polyethylene wadded, tamper evident, child resistant closure.
Pack: 150 ml oral solution

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Perrigo Pharma International Designated Activity Company
The Sharp Building

Hogan Place
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22741/010/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17May 2002
Date of last renewal: 5 December 2008

10 DATE OF REVISION OF THE TEXT

December 2020