SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tamoxifen Rosemont 10mg/5ml 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

4.1 Therapeutic indications

- The treatment of breast cancer
- The primary prevention of breast cancer in women at moderate or high risk (see section 5.1).

  Women aged less than 30 years old were excluded from primary prevention trials so the efficacy and safety of tamoxifen treatment in these younger women is unknown.

4.2 Posology and method of administration

Posology

Breast cancer

Adults:

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.

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 have been used in the elderly with breast cancer and in some of these patients it has been used as sole therapy.

Primary prevention of breast cancer

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

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

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

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

Paediatric Population
Children: Not applicable.
The safety and efficacy of tamoxifen in children has not yet been established (see sections 5.1 and 5.2).

Method of Administration
For oral use.

4.3 Contraindications

General contraindications (all indications)

Tamoxifen should not be used in:
- Pregnancy and lactation:
- Hypersensitivity to tamoxifen or to any of the excipients listed in section 6.1
- Concurrent anastrozole therapy (see section 4.5)

Primary prevention of breast cancer
Tamoxifen should not be used in:

• Women with a history of deep vein thrombosis or pulmonary embolus.
• Women who require concomitant coumarin-type anticoagulant therapy (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

The warnings and precautions for use are different depending on the indication being treated. The specific warnings and precautions for the primary prevention of breast cancer can be found at the end of the section.

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; 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.

There are several factors that influence the risk of developing endometrial cancer, with the majority of risk factors affecting oestrogen levels. Therefore, tamoxifen 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 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 investigation due 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: For patients with breast cancer 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.

• All 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 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.

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.

Additional precautions relating to primary reduction of breast cancer risk

Tamoxifen therapy for this indication has uncommonly been associated with serious side effects such as pulmonary embolus and uterine cancer (both endometrial adenocarcinoma and uterine sarcoma). In trials comparing tamoxifen to placebo for reduction of the incidence of breast cancer in women at increased risk of breast cancer, the use of tamoxifen was associated with an increased risk of serious and sometimes fatal adverse events including endometrial cancer (approximately 4 cases per 1000 women over 5 years of use) and thromboembolic events (including deep vein thrombosis and pulmonary embolism). Less serious side effects such as hot flushes, vaginal discharge, menstrual irregularities and gynaecological conditions may also occur. Non-gynaecological conditions such as cataracts were also increased (see section 4.8). Whether the benefits of treatment are considered to outweigh the risks depends on the woman's age, health history, and level of breast cancer risk (see sections 4.4, 4.8 and 5.1).

In the primary prevention studies, due to the limited number of patients with a confirmed BRCA mutation there is uncertainty about the absolute benefit in these patients treated with tamoxifen for primary prevention of breast cancer.

Benign gynaecological conditions (including endometrial polyps, endometriosis, and ovarian cysts) and gynaecological procedures (including hysteroscopy, dilation and curettage, and hysterectomy) were also found to occur more frequently with tamoxifen use.

Any women receiving or having previously received Tamoxifen for risk reduction should be promptly investigated if any abnormal gynaecological symptoms develop, especially non-menstrual vaginal bleeding.

The risks of tamoxifen therapy are generally lower in younger women than in older women. In the primary prevention trials, in contrast to women aged 50 years or older, women younger than 50 years did not have an increased risk of endometrial cancer or pulmonary embolism and the increased risk of deep vein thrombosis was small and restricted to the treatment period.

When considered for primary reduction of breast cancer risk, Tamoxifen is contraindicated in women who require concomitant coumarin-type anticoagulant therapy or in women with a history of deep vein thrombosis or pulmonary embolus (see sections 4.3 and 4.5). In women who do not have a history of thromboembolic events, but who are at increased risk of thromboembolic events, the benefits and risks of tamoxifen for the primary reduction of breast cancer risk should be carefully considered. Risk factors for thromboembolic events include smoking, immobility and a family history of venous thrombosis; an additional risk factor, is concomitant oral contraceptive or hormone replacement therapy, which is not recommended in women taking tamoxifen. In women receiving tamoxifen for primary reduction of breast cancer risk, tamoxifen should be stopped approximately 6 weeks before undergoing elective surgery to reduce the risk of thromboembolic events. Consideration should also be given to discontinuing tamoxifen during periods of immobility.

Bone mineral density in premenopausal women

Studies in premenopausal women who were treated with tamoxifen for reduction of breast cancer risk or in the management of breast cancer have reported decreases in bone mineral density. Premenopausal women taking Tamoxifen should be advised regarding measures to maintain bone health, according to local clinical guidelines.

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 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.

Exacerbation of hereditary angioedema

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

QT interval prolongation

Tamoxifen at the recommended dose, may prolong the QTc interval on the electrocardiogram (ECG).

ECG and electrolyte monitoring are recommended in patients with underlying risks of QT prolongation and cardiac comorbidities such as:

- Long QT syndrome
- Clinically significant or uncontrolled heart disease, such as congestive heart failure, recent myocardial infarction and cardiac conduction and repolarization abnormalities
- Concomitant use of QT prolonging medicines
- Electrolyte abnormalities

ECG should be assessed before initiating treatment and follow-up ECG should be repeated once tamoxifen has reached steady state concentrations (at least 4 weeks). ECG monitoring thereafter should be done as clinically indicated for patient-specific risk factors, i.e. introduction or dose changes of QT prolonging medicines, electrolyte abnormalities, new symptoms (e.g. palpitations, dizziness, syncope). Appropriate monitoring of serum electrolytes (including potassium, magnesium, calcium, phosphate) should be performed before initiating treatment and during treatment as clinically indicated. Any abnormalities should be corrected prior to initiating tamoxifen and during treatment.

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 interaction

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 cytotoxics are used in combination with tamoxifen solution 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.

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 3A4, 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).

QT interval prolongation:
Tamoxifen at the recommended dose may prolong the QTc interval on the electrocardiogram (ECG), and the concomitant use of Tamoxifen with other medicinal products known to prolong the QT interval may further potentiate QT prolongation. Therefore, caution is advised in case of such combination, and ECG and electrolyte monitoring are recommended in such patients (see section 4.4).

Primary prevention of breast cancer risk

In women receiving tamoxifen for the primary prevention of breast cancer, the use of coumarin type anticoagulants is contraindicated (see sections 4.3 and 4.4).

There is some evidence that hormone replacement therapy may reduce the effectiveness of tamoxifen, and the concomitant use of tamoxifen and oral hormonal contraceptives is not recommended. Therefore, the use of hormone replacement therapy or oral hormonal contraceptives to manage tamoxifen side effects is not recommended (see section 5.1).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Since the use of tamoxifen during pregnancy is contraindicated, women should be advised not to become pregnant whilst taking tamoxifen and within nine months after stopping tamoxifen medication 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 or within nine months of cessation of therapy.

Pregnancy:

Tamoxifen must not be administered during 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.

Reproductive toxicology studies in rats, rabbits and monkeys have shown no teratogenic potential.

Animal studies have shown reproduction toxicity (see section 5.3). 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 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. 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 the small number of young women known to have been exposed in utero to tamoxifen.

Breast-feeding:

Limited data suggest that tamoxifen and its active metabolites are excreted and accumulate over time in human milk. Therefore, tamoxifen treatment is contraindicated during breast-feeding. Tamoxifen inhibits lactation in humans and no rebound lactation was observed after completion of therapy.
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

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

Tamoxifen is unlikely to impair the ability of patients to drive or operate machinery.

Since fatigue, visual disturbances and light-headedness have been observed commonly with the use of tamoxifen, caution is advised when driving or using machines while such symptoms persist. 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 safety findings in the breast cancer prevention trials appeared consistent overall with the established safety profile of tamoxifen.

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 (including 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: 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 paraesthesia 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] , toxic epidermal necrolysis[a]
Very rare: Cutaneous lupus erythematosus[b]
Not known: Exacerbation of hereditary angioedema

Musculoskeletal and connective tissue disorders
Common: Leg cramp, myalgia
Not known: Decreased bone mineral density (premenopausal women)

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
Rare: Electrocardiogram QT prolonged.

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 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'.

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 (to not less than 20 mg/day) without loss of control of the disease. If undesirable events do not respond to this measure, it may be necessary to cease treatment.

Skin rashes (including rare reports of erythema 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.

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 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 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.

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) have been reported in association with tamoxifen treatment.

Primary prevention of breast cancer risk

The most common adverse events reported from studies in women at increased risk of breast cancer, and occurring more frequently during treatment with tamoxifen than with placebo, were those associated specifically with the pharmacological action of tamoxifen such as vasomotor symptoms (hot flushes, night sweats), menstrual abnormalities\irregularities, vaginal discharge, and vaginal dryness.

In the primary prevention trials tamoxifen significantly increased the incidence of endometrial cancer, deep vein thrombosis, and pulmonary embolism compared with placebo, but the absolute increase in risk was small. The risk of developing cataracts was also significantly increased with tamoxifen.

Women under 50 years old

A meta-analysis of risk reduction trials stratified by age showed that while women over 50 years old at randomisation had a significantly increased risk of endometrial cancer compared with placebo (RR 3.32, 95% CI 1.95-5.67; p<0.0001), women aged under 50 years did not (RR 1.19, 95% CI 0.53-2.65; p=0.6). Similarly, women under 50 years did not have a significantly increased risk of pulmonary embolism compared with placebo (RR 1.16, 95% CI 0.55-2.43; p=0.60) and their risk of deep vein thrombosis was only significantly increased during the active treatment phase (RR 2.30, 95% CI 1.23-4.31; p=0,009) but not after treatment had ended.

Gynaecological conditions and procedures

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

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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

5.1 Pharmacodynamic properties

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

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. 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.

An uncontrolled trial was undertaken in a heterogenous 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 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.

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.

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).

<u>CYP2D6 genotype</u>
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).

Primary reduction of breast cancer risk

Tamoxifen reduces but does not eliminate the risk of breast cancer. In clinical trials, Tamoxifen decreased the incidence of oestrogen receptor-positive tumours but did not alter the incidence of oestrogen receptor-negative tumours. The use of Tamoxifen should be as part of a program including regular breast surveillance tailored to the individual woman, taking into account her risk of breast cancer.

The breast cancer primary risk reduction trials include the International Breast Cancer Intervention Study (IBIS-1), the National Surgical Adjuvant Breast and Bowel Project PI study (NSABP P1), and the Royal Marsden Hospital chemoprevention trial (Royal Marsden). All trials were double-blind placebo controlled randomised trials of oral tamoxifen (20 mg per day) for the primary reduction of breast cancer risk in women at increased risk of breast cancer. Women were treated for 5 years (IBIS-1and NSABP P1) or 8 years (Royal Marsden) and followed for up to 20 years.

The IBIS-1, NSABP PI, and Royal Marsden trials all defined breast cancer risk differently, and recruited women with both moderate or high lifetime risk: IBIS-1 included women with a two-fold relative risk if they were aged 45 to 70 years, a fourfold relative risk if they were aged 40 to 44 years, or a ten-fold relative risk if they were aged 35 to 39 years; NSABP P1 included women aged ≥60 years or aged 35 to 59 years with a 5-year predicted risk for breast cancer of at least 1.66% as determined using a modified Gail's model or a history of Lobular Carcinoma In Situ (LCIS) or atypical hyperplasia; and Royal Marsden included healthy women aged 30 to 70 years old with an increased risk of developing breast cancer based on family history.

All trials excluded women with breast cancer (apart from Lobular Carcinoma In Situ - LCIS), a history of invasive cancer, pregnancy, and current or past deep vein thrombosis or pulmonary embolism. Other relevant exclusion criteria included the current use of oral contraceptives (NSABP P1, Royal Marsden), recent or current hormone replacement therapy (NSABP P1), and current anticoagulant use (IBIS-1).

The majority of women in all trials were aged 59 years or below. NSABP PI included the largest proportion of women aged 60 years or over (30%). In NSABP P1, the majority of women were white (96%); race was not reported in the other trials. A substantial proportion of women in all trials were premenopausa1 (46% in IBIS-1 and 65% in Royal Marsden) or younger than 50 years old (37% NSABP P1).

A summary of the key entry criteria for each of the trials are shown in Table 2.

Table 2 Summary of Key Criteria Used to Select Patients in Each of the Main Studies

Study	Key Entry Criteria
IBIS 1	Aged 35-70 years No previous invasive cancer (except non-melanoma skin cancer) Relative risk of developing breast cancer: • At least two-fold in women aged 45-70 • At least four- fold in women aged 40-44 • At least ten-fold in women aged 35-39 Calculated using a specifically designed model based on family history and standard risk factors
NSABP P1	Aged >35 years No clinical evidence of breast cancer 5-year predicted risk >1.66% of developing breast cancer based on the Gail model, or a history of LCIS or atypical hyperplasia based on a multivariable logistic regression model

STAR	Aged >35 years 5 yr predicted risk of >1.66% of developing breast cancer based on Gail model
Marsden	Aged 30 - 70 years old No clinical evidence of breast cancer Increased risk of developing breast cancer based on family history.

Efficacy results from the trials are shown in Table 3, which includes results of a meta-analysis of individual participant data from over 28,000 women who were treated with tamoxifen or placebo for the primary reduction of breast cancer risk. The results of the individual trials were generally consistent with the findings in the meta-analysis and the risk reduction effects of tamoxifen lasted for more than 10 years after treatment ended.

Table 3 Summary of Key Efficacy and Safety Results from the Primary Risk Reduction Trials

	Cuzick meta-analysis[a]		IBIS-1[b]		NSABP P1[c]		Royal Marsden[d]	
	Tamox n=14,192 Events	Placebo n=14,214 Events	Tamox n=3579 Events	Placebo n=3575 Events	Tamox n=6597 Events	Placebo n=6610 Events	Tamox n=1238 Events	Placebo n=1233 Events
Efficacy	HR (95% CI)		HR (95% CI)		RR (95% CI)		HR (95% CI)	
All breast cancer	431 (3.0%)	634 (4.5%)	251 (7.0%)	350 (9.8%)	205 (3.1%)	343 (5.2%)	96 (7.7%)	113 (9.1%)
	0.67 (0.59-0.76)		0.71 (0.60-0.83)		NR		0.84 (0.64-1.10)	
Invasive breast cancer	NR		214 (6.0%)	289 (8.1%)	145 (2.2%)	250 (3.8%)	82 (6.6%)	104 (8.4%)
			0.73 (0.61-0.87)		0.57 (0.46-0.70)		0.78 (0.58-1.04)	
Non-invasive cancers	77 (0.5%)	112 (0.8%)	35 (1.0%)	53 (1.5%)	60 (0.9%)	93 (1.4%)	14 (1.1%)	9 (0.7%)
	0.72 (0.57-0.92)		0.65 (0.43-1.00)		0.63 (0.45-0.89)		NR	
Oestrogen receptor-positive cancers	219 (1.5%)	396 (2.8%)	160 (4.5%)	238 (6.7%)	70 (1.1%)	182 (2.8%)	53 (4.2%)	86 (7.0%)
	0.56 (0.47-0.67)		0.66 (0.54-0.81)		0.38 (0.28-0.50)		0.61 (0.43-0.86)	

Oestrogen receptor-negative cancers	116 (0.8%)	103 (0.7%)	50 (1.4%)	47 (1.3%)	56 (0.8%)	42 (0.6%)	24 (1.9%)	17 (1.4%)
	1.13 (0.86-1.49)		1.05 (0.71-1.57)		1.31 (0.86-2.01)		1.4 (0.7-2.6)	
All cause mortality	1038 (2.3%*)	1050 (2.5%*)	182 (5.1%)	166 (4.6%)	126 (1.9%)	114 (1.7%)	54 (4.3%)	54 (4.3%)
	0·98* (0·90–1·06)		OR 1·10 (0·88–1·37)		RR 1.10 (0.85-1.43)		0.99 (0.68-1.44)	
Breast cancer mortality	30 (0.07%*)	29 (0.07%*)	31 (0.9%)	26 (1.0%)	12 (0.2%)	11 (0.2%)	12 (1.0%)	9 (0.7%)
	1.03* (0.55–1.92)		OR 1.19 (0.68–2.10)		NR		NR	

Safety	Events OR or RR (95% CI)							
Endometrial cancer	67 (0.5%)	31 (0.2%)	29 (0.8%)	20 (0.6%)	53 (0.8%)	17 (0.3%)	13 (1.0%)	5 (0.4%)
	OR 2.18 (95%CI 1.39-3.42)		OR 1.45 (95%CI 0.79-2.71)		RR 3.28 (95%CI 1.87-6.03)		NR	
Other cancers	787 (1.8%)	799 (1.9%)	322 (9.0%)	295 (8.3%)	NR		64 (5.1%)	70 (5.6%)
	OR 0.98* (95%CI 0.89-1.08)		NR				NR	
Venousthromboemblism (DVT,PE)	131 (0.9%)	82 (0.6%)	104 (2.9%)	62 (1.7%)	DVT 49 (0.7%) PE 28 (0.4%)	DVT 34 (0.5%) PE 13 (0.2%)	8 (0.6%)	3 (0.2%)
	OR 1.60 (95%CI 1.21-2.12)		OR 1.70 (95%CI 1.22-2.37)		DVT RR 1.44 (95%CI 0.91-2.30) PE RR 2.15 (95%CI 1.08-4.51)		NR	

Stroke	NR		30 (0.8%)	28 (0.8%)	71 (1.1%)	50 (0.8%)	7 (0.6%)	9 (0.7%)
			OR 1.07 (95%CI 0.62-1.86)		RR 1.42 (95%CI 0.97-2.08)		NR	
Fractures	731 (5.2%)	791 (5.6%)	240 (6.7%)	235 (6.6%)	80 (1.2%)	116 (1.8%)	19 (1.5%)	22 (1.8%)
	OR 0.92 (95%CI 0.83-1.02)		RR 1.02** (95%CI 0.86-1.21)		RR 0.68 (95%CI 0.51-0.92)		NR	

Abbreviations: CI = confidence interval, HR = hazard ratio, NS = nonsignificant, NR =not reported, placeb = placebo, RR = risk ratio, tamox = tamoxifen.

[a] Cuzick 2013 was a meta-analysis of individual participant data from the IBIS-I, NSABP P1, and Royal Marsden primary prevention trials in women at increased risk ofbreast cancer, and the Italian trial in women at normal risk of breast cancer. The medianfollow up was 65 months.

[b] Participants were treated with 20 mg tamoxifen for 5 years; the median follow up was16 years.

[c] Participants were treated with 20 mg tamoxifen for 5 years; the median follow up was6 years

[d] Participants were treated with 20 mg tamoxifen for 8 years; the median follow up was13 years

*This result is for all 9 studies included in the meta- analysis not just the tamoxifen studies, as it is not reported for just the tamoxifen studies. There was no heterogeneitybetween the studies for this category

** This result is after 8 years median follow up in the IBIS- 1 study, as not all adverse events continued to be recorded after this as no events were anticipated to occur more than 5 years after completion of treatment.

Mortality was a secondary outcome measure for the IBIS-1, NSABP P1 and Royal Marsden trials. In comparing the tamoxifen and placebo arms, no significant difference was found for mortality in each trial. This outcome may be due to confounding factors in these trials such as low event rates, underpowering, close screening leading to early detection of events and subsequent breast cancer treatments.

Concomitant use of Hormone Replacement Therapy

The IBIS-1 trial found that tamoxifen was effective in reducing the risk of breast cancer in women who were not taking hormone replacement therapy. For women who did use hormone replacement therapy, there was no significant reduction in the risk of

developing invasive breast cancers: 110 vs 124 (HR 0.88, 95% CI 0.68- 1.13, p=0.31). These findings were consistent over the 20-year study period. In the NSABP P1 trial, women who were taking hormone replacement therapy were excluded from the trial. The Royal Marsden trial was not powered to demonstrate an effect. Therefore, the concomitant use of tamoxifen and hormone replacement therapy is not recommended for primary prevention of breast cancer.

Effects of age and menopausal status

No age-related effects of tamoxifen on breast cancer incidence were reported in the primary risk reduction trials. Analyses according to age were performed in the final analyses of the IBIS-1 and the NSABP P1 trials. In the IBIS-1 trial, breast cancer incidence was significantly decreased in the tamoxifen vs the placebo group in women aged ≤50 years and >50 years, In the NSABP P1 trial, invasive breast cancer incidence was significantly decreased in the tamoxifen vs the placebo group in women aged ≤49 years, 50 to 59 years, and ≥60 years. Thus, no

age-related effects of tamoxifen on breast cancer incidence were reported in the trials.

Analyses according to menopausal status were performed in the 96-month analysis of the IBIS-1 trial. In the IBIS-1 trial, tamoxifen significantly reduced the risk of breast cancer in premenopausal women compared with placebo. It should be noted that the IBIS-1 trial was not sufficiently powered to detect a difference specifically in postmenopausal women. In the NSABP P1 trial, the incidence of invasive breast cancer was significantly lower in the tamoxifen vs placebo group in women aged ≥60 years, who would have been postmenopausal (40 vs 80, RR 0.49, 95% CI0.33-0.73).

Lobular carcinoma in situ and atypical hyperplasia

In NSABP P1, there was a 75% breast cancer risk reduction in women with a history of atypical hyperplasia compared with a 37% risk reduction in women with no history of atypical hyperplasia (RR 0.63, 95% CI 0.50-0.78). The risk reductions for women with and without lobular carcinoma in situ were similar.

5.2 Pharmacokinetic properties

Absorption:
After oral administration tamoxifen is rapidly 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 40 mg daily therapy, it was

observed that steady state serum levels (about 300ng/ml) 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.

In a clinical study where girls between 2 and 10 years with McCune Albright Syndrome (MAS) received 20mg 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.

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.

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.

6.1 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 the container

Bottle: Amber (Type III) glass
Closure: HDPE, polyethylene wadded, tamper evident, child resistant closure.

Pack: 150ml 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

Rosemont Pharmaceuticals Ltd
Rosemont House
Yorkdale Industrial Park
Braithwaite Street
Leeds
LS11 9XE
UK

8. MARKETING AUTHORISATION NUMBER

PL 00427/0121

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 16 August 1999
Date of last renewal: 27 November 2004

10 DATE OF REVISION OF THE TEXT

12/05/2026