Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Moxelle 20mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30.4mg tamoxifen citrate equivalent to 20mg tamoxifen.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Round, white, biconvex tablets with a score line and ‘TN20’ embossed on one side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Moxelle 20mg Tablets are indicated for the treatment of breast cancer.

4.2 Posology and method of administration

Route of administration: ORAL

1. Breast cancer

Adults
The recommended daily dose of tamoxifen is normally 20mg. 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 patients
Similar dosing regimens of Moxelle 20mg Tablets have been used in elderly patients with breast cancer and in some of these patients it has been used as sole therapy.

4.3 Contraindications

Moxelle 20mg Tablets must not be given during pregnancy. Pre-menopausal patients must be carefully examined before treatment for breast cancer or infertility to exclude the possibility of pregnancy (see also Section 4.6).

Moxelle 20mg Tablets should not be given to patients who have experienced hypersensitivity to the product or any of its ingredients.

Treatment for infertility: Patients with a personal or family history of confirmed idiopathic venous thromboembolic events or a known genetic defect.

4.4 Special warnings and precautions for use

Menstruation is suppressed in a proportion of pre-menopausal women receiving Moxelle 20mg Tablets for the treatment of breast cancer.

An increased incidence of endometrial changes including hyperplasia, polyps, cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours), has been reported in association with Moxelle 20mg Tablets treatment. The underlying mechanism is unknown but may be related to the oestrogen-like effect properties of Moxelle 20mg Tablets. Any patient receiving or having previously received Moxelle 20mg Tablets who report abnormal gynaecological symptoms, especially vaginal bleeding, or who presents with menstrual irregularities, vaginal discharge and symptoms such as pelvic pain or pressure should be promptly investigated.

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

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 (cross-reference section 4.5).
- The risk of VTE is further increased by severe obesity, increasing age and all other risk factors for VTE. The risks and benefits should be carefully considered for *all* patients before treatment with Tamoxifen. In patients with *breast cancer*, this risk is also increased by concomitant chemotherapy (see section 4.5). Long-term anti-coagulant prophylaxis may be justified for some patients with *breast cancer* who have multiple risk factors for VTE.
- Surgery and immobility: Tamoxifen should be stopped at least 6 weeks before surgery or long-term immobility (when possible) and re-started only when the patient is fully mobile. 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 anti-coagulant treatment.
- If *any* patients with VTE, tamoxifen should be stopped immediately and appropriate anti-thrombosis measures initiated. Tamoxifen should not be restarted unless there is a compelling alternative explanation for their thrombotic event. In patients receiving tamoxifen for *breast cancer,* the decision to re-start tamoxifen should be made with respect to the overall risk for the patient. In selected patients with *breast cancer,* the continued use of Tamoxifen with prophylactic anticoagulation may be justified.

All patients should be advised to contact their doctors immediately if they become aware of any symptoms of VTE.
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

When Moxelle 20mg Tablets are used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur.

Where such co-administration is initiated, careful monitoring of the patient is recommended.

When Moxelle 20mg Tablets are used in combination with cytotoxic agents for the treatment of breast cancer, there is increased risk of thromboembolic events occurring. (See also Sections 4.4 and 4.8). Because of this increase in risk of VTE, thrombosis prophylaxis should be considered for these patients for the period of concomitant chemotherapy.

As Moxelle 20mg Tablets are metabolised by cytochrome P450 3A4, care is required when co-administering with drugs, such as rifampicin, known to induce this enzyme as tamoxifen levels may be reduced. The clinical relevance of this reduction is unknown.

Pharmacokinetic interaction with CYP2D6 inhibitors, showing a 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

Moxelle 20mg Tablets 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 Moxelle 20mg Tablets, although no causal relationship has been established.

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

In rodent models of foetal reproductive tract development, tamoxifen was associated with changes similar to those caused by oestradiol, ethynyloestradiol, clomiphene and diethylstilboestrol (DES). Although the clinical relevance of these changes is unknown, some of them, especially vaginal adenosis, are similar to those seen in young women who were exposed to DES in-utero and who have a 1 in 1000 risk of developing clear-cell carcinoma of the vagina or cervix. Only a small number of pregnant women have been exposed to tamoxifen. Such exposure has not been reported to cause subsequent vaginal adenosis or clear-cell carcinoma of the vagina or cervix in young women exposed in utero to tamoxifen.

Women should be advised not to become pregnant whilst taking Moxelle 20mg Tablets and should use barrier or other non-hormonal contraceptive methods if sexually active. Pre-menopausal 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 20mg Tablets or within two months of cessation of therapy.

Lactation

It is not known if Moxelle 20mg Tablets are excreted in human milk and therefore the drug is not recommended during lactation. The decision either to discontinue nursing or discontinue Moxelle 20mg Tablets should take into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

There is no evidence that Moxelle 20mg Tablets result in impairment of these activities.

4.8 Undesirable effects

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. gastro-intestinal intolerance, headache, light-headedness and occasionally, fluid retention and alopecia.

When side effects are severe, it may be possible to control them by a simple reduction of dosage (to not less than 20mg/day) without loss of control of the disease. If side effects do not respond to this measure, it may be necessary to stop the treatment.

Skin rashes (including isolated reports of erythema multiforme, Stevens- Johnson syndrome and bullous pemphigoid) and rare hypersensitivity reactions including angioedema have been reported.

A small number of patients with bony metastases have developed hypercalcaemia on initiation of therapy.

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.

A number of cases of visual disturbance including reports of corneal changes and retinopathy have been described in patients receiving Moxelle 20mg Tablets. An increased incidence of cataracts has been reported in association with the administration of Moxelle 20mg Tablets.

Uterine fibroids, endometriosis and other endometrial changes including hyperplasia and polyps have been reported.

Cystic ovarian swellings have occasionally been observed in pre-menopausal women receiving Moxelle 20mg Tablets.

Leucopenia has been observed following the administration of Moxelle 20mg Tablets, sometimes in association with anaemia and/or thrombocytopenia. Neutropenia has been reported on rare occasions; this can sometimes be severe.

Cases of deep vein thrombosis and pulmonary embolism have been reported during Tamoxifen therapy (see sections 4.3, 4.4 and 4.5.). When Moxelle 20mg Tablets are used in combination with cytotoxic agents, there is an increased risk of thrombo-embolic events.

Very rarely, cases of interstitial pneumonitis have been reported.

Moxelle 20mg Tablets have been associated with changes in liver enzyme levels and on rare occasions with a spectrum of more severe liver abnormalities including fatty liver, cholestasis and hepatitis.

Rarely, elevation of serum triglyceride levels, in some cases with pancreatitis, may be associated with the use of Moxelle 20mg Tablets.

An increased incidence of endometrial cancer and uterine sarcoma (mostly malignant mixed Mullerian tumour) has been reported in association with Moxelle 20mg Tablets treatment.

4.9 Overdose

On theoretical grounds, an overdosage would be expected to cause enhancement of the pharmacological side effects mentioned above. Observations in animals show that extreme overdosage (100 – 200 times recommended daily dose) may produce oestrogenic effects.

There is no specific antidote to overdosage, and treatment must be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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. However, clinical studies have shown some benefit in oestrogen receptor negative tumours which may indicate other mechanisms of action. In the clinical situation, it is recognised that tamoxifen leads to reductions in levels of blood total cholesterol and low density lipoproteins in postmenopausal women of the order of 10 – 2- % Tamoxifen does not adversely affect

bone mineral density.
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 40mg daily. The drug is highly protein bound to serum albumin (> 99%). Metabolism is by hydroxylation, demethylation and conjugation, giving rise to several metabolites which have a similar pharmacological profile to the parent compound and thus contribute to the therapeutic effect. Excretion occurs primarily via the faeces and an elimination half-life of approximately seven days has been calculated for the drug itself, whereas that for N-desmethyltamoxifen, the principal circulating metabolite, is 14 days.

Tamoxifen is metabolised mainly via CYP3A4 to N-desmethyl-tamoxifen, which is further metabolised by CYP2D6 to another active metabolite endoxifen. In patients who lack the enzyme CYP2D6 endoxifen concentrations are approximately 75% lower than in patients with normal CYP2D6 activity. Administration of strong CYP2D6 inhibitors reduces endoxifen circulating levels to a similar extent.

5.3 Preclinical safety data

Tamoxifen was not mutagenic in a range of in-vitro and in-vivo mutagenicity tests. Tamoxifen was genotoxic in some in-vitro and in-vivo genotoxicity tests in rodents. Gonadal tumours in mice and liver tumours in rats receiving Tamoxifen have been reported in long-term studies. The clinical relevance of these findings has not been established.

Tamoxifen is a drug on which extensive clinical experience has been obtained. Relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium Hydrogen Phosphate
Microcrystalline Cellulose
Sodium Starch Glycolate (Type A)
Povidone (K25)
Magnesium Stearate
Silica, Colloidal Anhydrous

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

Two years.

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Blister strips (20µm aluminium foil / 250µm PVC film dark green coloured)

Blister strips of 10 tablets. Pack size: 30 and 250 tablets.

Not all pack 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

Relon Chem Limited
27, Old Gloucester Street
London
WC1 3XX
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1128/008/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 12th June 2009

Date of last renewal:12th June 2014

10 DATE OF REVISION OF THE TEXT

February 2014