NEW ZEALAND DATA SHEET
TAMOXIFEN SANDOZ (TAMOXIFEN CITRATE) FILM-COATED TABLETS

1. PRODUCT NAME

Tamoxifen Sandoz

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tamoxifen Sandoz 10 mg: Each tablet contains tamoxifen citrate equivalent to tamoxifen 10 mg.

Tamoxifen Sandoz 20 mg: Each tablet contains tamoxifen citrate equivalent to tamoxifen 20 mg.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

10 mg: Tablet, film coated, 7 mm round, white, biconvex, plain both sides.

20 mg: Tablet, film coated, 9 mm round, white, biconvex, plain one side and scored on the other.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Tamoxifen Sandoz is indicated for the treatment of breast cancer; the response is similar to that seen with either estrogens or androgens but tamoxifen appears to produce less marked side-effects and to be more acceptable to the patient.

4.2. DOSE AND METHOD OF ADMINISTRATION

Dosage

Adults (including the elderly)

Breast cancer

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

Children

Tamoxifen is not indicated for use in children.

Method of administration

For oral administration.

4.3. CONTRAINDICATIONS

Tamoxifen must not be administered during pregnancy. Premenopausal patients must be carefully examined before treatment for breast cancer to exclude the possibility of pregnancy. There have been a small number of reports of spontaneous abortions, birth defects and foetal

deaths after women have taken tamoxifen, although no causal relationship has been established (refer to Section 4.4 Special warnings and precautions for use).

Tamoxifen should not be given to patients who have experienced hypersensitivity to the product or any of its ingredients.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Menstruation is suppressed in a proportion of pre-menopausal women receiving tamoxifen 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 tamoxifen treatment. The incidence and pattern of this increase suggest that the underlying mechanism is related to the oestrogenic properties of tamoxifen. Any patients receiving or having previously received tamoxifen, who report abnormal gynaecological symptoms, especially non-menstrual vaginal bleeding, should be promptly investigated. Any patients receiving or having previously received tamoxifen, should be asked to report promptly to their doctor the following signs and symptoms which may be suggestive of the presence of endometrial cancer: abnormal vaginal bleeding such as bleeding between periods, heavier than normal bleeding, bleeding after menopause; changes in vaginal discharge; lower abdominal pain or pressure. These patients should be promptly investigated.

According to one study, women who have taken unopposed estrogen therapy, who are obese, or who are continuing to take tamoxifen after therapy for more than 5 years may be at greater risk for endometrial cancer and consideration should be given to closer monitoring of these groups.

In a large randomised trial in Sweden of adjuvant tamoxifen 40 mg/day for 2-5 years, an increased incidence of uterine cancer was noted. Twenty three of 1,372 patients randomised to receive tamoxifen versus 4 of 1,357 patients randomised to the observation group developed cancer of the uterus [RR=5.6; 1.9-16.2), $p < 0.001$].

One of the patients with cancer of the uterus who was randomised to receive tamoxifen never took the drug. After approximately 6.8 years of follow-up in the ongoing NSABP (National Surgical Adjuvant Breast and Bowel Project) B-14 trial, 15 of 1,419 women randomised to receive tamoxifen 20 mg/day for five years developed uterine cancer, and 2 of the 1,424 women randomised to receive placebo, who subsequently had recurrent breast cancer and were treated with tamoxifen, also developed uterine cancer. Most of the uterine cancers were diagnosed at an early stage, but deaths from uterine cancer have been reported. Patients receiving tamoxifen should have routine gynaecological care and report any abnormal vaginal bleeding to their doctor.

(The NSABP B-14 trial is undergoing reaudit and information from this study may be subject to change).

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

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

There is evidence of an increased incidence of thromboembolic events, including deep vein thrombosis and pulmonary embolism, during Tamoxifen Sandoz therapy. When Tamoxifen Sandoz is co-administered with chemotherapy, there may be a further increase in the incidence of thromboembolic effects. For treatment of breast cancer, the risks and benefits of Tamoxifen Sandoz should be carefully considered in women with a history of thromboembolic events.

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

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.

Retinopathy and keratopathy may occur and patients should be asked to report the following symptoms of ocular damage without delay: blurred vision lasting more than 2 weeks; change in colour vision. Patients reporting these symptoms should be referred for ophthalmological examination. The ocular damage caused by tamoxifen is characterised by a reduction in visual acuity, bilateral macular oedema and yellow ring-like deposits in the paramacular and fovea areas. If tamoxifen is withdrawn promptly the vision usually returns to normal without permanent impairment.

Cases of visual disturbances, including infrequent reports of corneal changes, and common reports of retinopathy have been described in patients receiving tamoxifen therapy. Cataracts have commonly been reported in association with the administration of tamoxifen.

Tamoxifen should be used cautiously in patients with existing leucopenia or thrombocytopenia. Leucopenia has been observed following the administration of tamoxifen, sometimes in association with anaemia and/or thrombocytopenia. Neutropenia has been reported on rare occasions and can sometimes be severe and rarely cases of agranulocytosis have been reported. Decreases in platelet counts (usually to 50,000 to 100,000/mm^3, infrequently lower) have been occasionally reported in patients taking tamoxifen for breast cancer. Periodic complete blood counts, including platelet counts, may be appropriate.

Tamoxifen Sandoz at the recommended dose may prolong the QTc interval on the electrocardiogram (ECG) in patients with underlying risks for QT prolongation and cardiac comorbidities. ECG and electrolyte monitoring are recommended in such patients.

Poor metabolisers of CYP2D6 may have a reduced response to tamoxifen due to reduced plasma concentrations of the active metabolite, endoxifen.

Concomitant medicines that inhibit CYP2D6 may reduce the concentration of the active tamoxifen metabolite, endoxifen. Some studies have shown reduced efficacy of tamoxifen as measured by the risk of breast cancer recurrence and mortality, when taken with CYP2D6 inhibitors. Common CYP2D6 inhibitors include paroxetine, fluoxetine and bupropion. Women taking tamoxifen should avoid using CYP2D6 inhibitors wherever possible *(*see Section 4.5 Interactions with other medicines and other forms of interactions).

Use in premenopausal women

It should be noted that only a small number of premenopausal women have been treated, since candidates for therapy are usually postmenopausal, either reaching a natural menopause, or having menopause induced by surgery or radiotherapy. Menstruation is suppressed in a

proportion of premenopausal women receiving tamoxifen for the treatment of breast tumours. Ovarian cysts have occasionally been observed in women receiving tamoxifen.

The use of tamoxifen for reduction of breast cancer risk or for breast cancer treatment may reduce the bone mineral density in premenopausal women. Premenopausal women taking Tamoxifen Sandoz for this reason should be advised regarding measures to maintain bone health.

Use in the elderly

See Section 4.2 Dose and method of administration.

Paediatric use

See Section 4.2 Dose and method of administration.

Effects on laboratory tests

No data available.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

When tamoxifen is 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 tamoxifen is used in combination with cytotoxic agents, there is increased risk of thromboembolic events occurring. (Refer to Section 4.8 Undesirable effects).

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

The known principal pathway for tamoxifen metabolism in humans is demethylation, catalysed by CYP3A4 enzymes. Pharmacokinetic interactions with the CYP3A4 inducing agent rifampicin, showing a reduction in tamoxifen plasma levels have been reported in the literature.

Pharmacokinetic interaction between CYP2D6 inhibitors and tamoxifen has been reported in the literature. This showed a reduction in plasma level of active tamoxifen metabolite, 4-hydroxy-N-desmethyltamoxifen. Reduced efficacy on tamoxifen has been reported with concomitant usage of some SSRI antidepressants (e.g. paroxetine).

CYP2D6

Cytochrome P450 2D6 (CYP2D6) plays an important role in the metabolism of tamoxifen. CYP2D6 helps convert tamoxifen to endoxifen (a potent active metabolite of tamoxifen). Therefore, co-administration of tamoxifen with CYP2D6 inhibitors (such as paroxetine, fluoxetine and bupropion) may reduce plasma levels of endoxifen and should be avoided where possible (see Section 4.4 Special warnings and precautions for use).

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Effects on reproductive functions are expected from the anti-estrogenic properties of the medicine. In the rat, uterine pressure effects (deformation of rib cage and altered cranial ossification patterns) have been ascribed to inhibition of the action of estrogens on the uterus,

but these simple deformations disappear after birth. In pregnant marmosets dosed during organogenesis or in the last half of pregnancy, no deformations were seen.

Use in pregnancy

Category B3

Tamoxifen Sandoz must not be administered during pregnancy. There have been a small number of reports of spontaneous abortions, birth defects and fetal deaths after women have taken tamoxifen, although no causal relationship has been established (see section 4.3 Contraindications).

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 estradiol, ethinylestradiol, clomiphene and diethylstilbestrol (DES). Although the clinical relevance of these changes is unknown, some of them, especially vaginal adenosis, are similar to those seen in young women who were exposed to DES *in utero* and who have a 1 in 1000 risk of developing clear-cell carcinoma of the vagina or cervix. Only a small number of pregnant women have been exposed to tamoxifen. Such exposure has not been reported to cause subsequent vaginal adenosis or clear-cell carcinoma of the vagina or cervix in young women exposed *in utero* to tamoxifen.

Women should be advised not to become pregnant whilst taking tamoxifen and for nine months following the cessation of therapy and should use barrier or other non-hormonal contraceptive methods if sexually active.

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

Use in lactation

It is not known if tamoxifen is excreted in human milk and therefore the medicine is not recommended during lactation.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Fatigue has been reported with the use of Tamoxifen Sandoz. Therefore, caution should be observed when driving or operating machinery while such symptoms persist.

4.8. UNDESIRABLE EFFECTS

The adverse reactions which have been reported are of two types: those associated specifically with the pharmacological action of the drug, e.g. hot flushes, vaginal bleeding, vaginal discharge, pruritus vulvae, tumour pain and tumour flare; and those of a more general nature, e.g. gastrointestinal intolerance, headache, light-headedness, and occasionally, fluid retention and alopecia. In patients treated with tamoxifen for metastatic breast cancer the most frequent adverse reactions are hot flushes, nausea and vomiting. These may occur in up to 25% of patients. Less frequently reported adverse reactions are vaginal bleeding, vaginal discharge, menstrual irregularities, alopecia and increased bone and tumour pain. Other adverse reactions which are seen infrequently are hypercalcaemia, peripheral oedema, pruritus vulvae, dizziness and light-headedness. Infrequent cases of endometrial, ocular and haematological adverse effects have been reported (see Section 4.4 Special warnings and precautions for use).

When such adverse reactions are severe, it may be possible to control them by a simple reduction of dosage (within the recommended dose range) without loss of control of the disease. If adverse reactions 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, toxic epidermal necrolysis, cutaneous vasculitis and bullous pemphigoid) and commonly hypersensitivity reactions, including angioedema have been reported.

Cases of exacerbation of angioedema have been reported in patients with hereditary angioedema receiving tamoxifen.

Although hypercalcaemia may occur in patients with advanced breast cancer, uncommonly patients with bony metastases developed hypercalcaemia on initiation of therapy.

Cases of optic neuropathy and optic neuritis have been rarely reported in patients receiving tamoxifen and, in a small number of cases, blindness has occurred.

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

Cystic ovarian swellings have occasionally been observed in women receiving tamoxifen. Vaginal polyps have rarely been observed in women receiving tamoxifen.

An increased incidence of endometrial cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours) has been reported in association with tamoxifen treatment.

There is evidence of an increased incidence of ischaemic cerebrovascular events and thromboembolic events, including deep vein thrombosis, microvascular thrombosis and pulmonary embolism, occurring commonly during tamoxifen therapy. When tamoxifen is used in combination with cytotoxic agents, there is a further increase in the risk of thromboembolic events occurring.

Leg cramps and myalgia have been reported commonly with 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, hepatitis, liver failure, cirrhosis and hepatocellular injury (including hepatic necrosis).

Depression has been reported with frequency very common in association with the use of 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.

Sensory disturbances (including paraesthesia and dysgeusia) have been reported commonly 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.

Commonly, elevation of serum triglyceride levels, in some cases with pancreatitis, may be associated with the use of tamoxifen.

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9. OVERDOSE

Signs and symptoms

On theoretical grounds, an overdosage would be expected to cause an enhancement of the pharmacological side-effects. Animal studies have shown that extreme overdosage (100 to 200 times the recommended daily dose) may produce estrogenic effects.

There have been reports in the literature that tamoxifen given at several times the standard dose may be associated with prolongation of the QT interval of the ECG.

Management

There is no specific antidote and treatment must be symptomatic.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group

L02BA01 – Antiestrogens, tamoxifen.

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 to 20%. Additionally, tamoxifen has been reported to lead to maintenance of bone mineral density in postmenopausal women.

Mechanism of action

Tamoxifen is a non-steroidal, triphenylethylene-based drug, which displays a complex spectrum of estrogen antagonist and estrogen agonist-like pharmacological effects in different tissues.

In breast cancer patients, at the tumour level, tamoxifen acts primarily as an antiestrogen, preventing estrogen binding to the estrogen receptor. In women with estrogen receptor-positive/unknown breast tumours, adjuvant tamoxifen has been shown to significantly reduce recurrence of the disease and improve 10 year survival, achieving a significantly greater effect with five years treatment than with 1 or 2 years treatment. These benefits appear to be largely irrespective of age, menopausal status, tamoxifen dose and additional chemotherapy. However, clinical studies have also shown some benefit in oestrogen receptor negative tumours in patients both with early and advanced disease, which may indicate other mechanisms of action.

Clinical trials

No data available.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

Tamoxifen is absorbed from the gastrointestinal tract, however the site and extent of absorption is not known. Peak serum levels of 15 to 25 nanogram/mL were observed three to six hours after administration of a single oral dose of tamoxifen 10 mg. Steady state serum levels are achieved after approximately four weeks of therapy. Mean steady state values after dosing at 20 mg twice daily were 285 +/- 19 nanogram/mL and 477 +/- 35 nanogram/mL for tamoxifen and N-desmethyltamoxifen respectively.

Bioavailability

No information available.

Distribution

Little information is available in humans. It has been found in the uterus and ovary, particularly in the endometrium and corpus luteum. Radioactivity studies in animals show high levels in the liver, lung, ovary and spleen. Low levels have been found in the pituitary, eyes and brain.

Protein binding

Tamoxifen appears to be bound to an unknown degree to cytoplasmic protein receptors in all oestrogen target tissues, and is highly protein bound to serum albumin (> 99%).

Metabolism

Tamoxifen undergoes extensive metabolism in the liver by hydroxylation, demethylation and conjugation, giving rise to several metabolites. The major circulating metabolite of tamoxifen in humans is N-desmethyltamoxifen which has a pharmacological profile very similar to that of tamoxifen and thus contributes to the therapeutic effect. Other minor metabolites are formed, some of which also have antioestrogenic activity.

Excretion

The elimination of tamoxifen and its major metabolite N-desmethyltamoxifen is slow. This leads to extensive accumulation of both compounds in serum during chronic administration. Tamoxifen is mainly excreted via the faeces, with only small amounts appearing in the urine. The drug is excreted mainly as conjugates. In one patient studied for 13 days after dosing, approximately 50% of the dose had been excreted in the faeces, and 13% in the urine. Tamoxifen undergoes enterohepatic circulation in animals, and is thought to do so in humans.

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

Half-life

The elimination half-life of tamoxifen is estimated to be 5 to 7 days and 10 to 14 days for N-desmethyltamoxifen.

Clinical implications of pharmacokinetic data

As the main site of metabolism is the liver, and accumulation of the drug and its active metabolites is possible with prolonged treatment, dose and dosing interval may need adjustment in patients with hepatic disease.

5.3. PRECLINICAL SAFETY DATA

Genotoxicity

No mutagenic effects have been seen. Tamoxifen was not mutagenic in a range of *in vitro* and *in vivo* mutagenicity tests. Tamoxifen was genotoxic in some *in vitro* tests 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 significance of these findings has not been established.

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Lactose, microcrystalline cellulose, sodium starch glycollate, povidone, magnesium stearate, hypromellose, titanium dioxide, macrogol 4000.

6.2. INCOMPATIBILITIES

None known.

6.3. SHELF LIFE

36 months from date of manufacture.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light and moisture.

6.5. NATURE AND CONTENTS OF CONTAINER

Packs of 60 tablets in cartoned blister strips. Not all pack sizes and/or strengths may be currently marketed.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

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

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Sandoz New Zealand Limited
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Telephone: 0800 726 369

9. DATE OF FIRST APPROVAL

09 December 2014

10. DATE OF REVISION OF THE TEXT

13 October 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Minor editorial changes Safety update to include warning for premenopausal women with potential reduction in bone mineral density
4.9	Added risk assessment wording