

Tamoxifen Sandoz

Tamoxifen Citrate Ph Eur, film coated tablet, 10 mg and 20 mg (as tamoxifen)

Presentation

10 mg

Tablet, film coated, 7 mm round, white, biconvex, plain both sides. Each tablet contains tamoxifen citrate equivalent to tamoxifen 10 mg.

20 mg

Tablet, film coated, 9 mm round, white, biconvex, plain one side and scored on the other. Each tablet contains tamoxifen citrate equivalent to tamoxifen 20 mg.

Uses

Actions

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.

Pharmacotherapeutic group

L02BA01 – Antiestrogens, tamoxifen.

Mechanism of action

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.

Pharmacodynamic effects

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.

Pharmacokinetics

Absorption

After oral administration, tamoxifen is absorbed rapidly with maximum serum concentrations attained within 4 to 7 hours. Steady state concentrations (about 300 nanogram/ml) are achieved after four weeks treatment with 40 mg daily.

Distribution

The medicine is highly protein bound to serum albumin (>99%).

Biotransformation

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.

Elimination

Excretion occurs primarily via the faeces and an elimination half-life of approximately seven days has been calculated for the medicine itself, whereas that for N-desmethyltamoxifen, the principal circulating metabolite, is 14 days.

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.

Dosage and 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.

Endometrial cancer

The dosage range is 20 to 40 mg daily given either in divided doses twice daily or as a single dose once daily.

Children

Tamoxifen is not indicated for use in children.

Contraindications

Tamoxifen must not be administered during pregnancy. There have been a small number of reports of spontaneous abortions, birth defects and foetal deaths after women have taken tamoxifen, although no causal relationship has been established (refer to [Warnings and precautions](#)).

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

Warnings and precautions

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

Endometrial cancer An increased incidence of endometrial cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours) has been reported in association with tamoxifen treatment. The underlying mechanism is unknown, but may be related to the estrogen-like effect of tamoxifen. Any patients receiving or having previously received tamoxifen, who report abnormal gynaecological symptoms, especially 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.

Retinopathy

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.

CYP2D6

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 Interactions section*).

Use in pregnancy

Assigned Category B3 by the Australian Drug Evaluation Committee. This category includes medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

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 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 two 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. The decision either to discontinue nursing or discontinue tamoxifen should take into account the importance of the medicine to the mother.

Effects on ability to drive and use machines

This medicine is presumed to be safe or unlikely to produce an effect. There is no evidence that tamoxifen results in impairment of these activities.

Carcinogenesis, Mutagenesis, Impairment of fertility

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.

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.

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.

Adverse effects

During long-term treatment, side-effects are not as numerous or as serious with tamoxifen as with the androgens and estrogens which are also used to treat breast cancer. Those that have been reported can be classified as either due to the pharmacological action of the medicine, e.g. hot flushes, vaginal bleeding, vaginal discharge and pruritus vulvae and tumour flare or as more general side-effects, e.g. gastro-intestinal intolerance, headache, lightheadedness, and, occasionally, fluid retention and alopecia.

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

Uncommonly, patients with bony metastases developed hypercalcaemia on initiation of therapy.

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. 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.

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

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; this can sometimes be severe and rarely cases of agranulocytosis have been reported. Falls in platelet count, usually only to 50,000 to 100,000/cubic millimetre, but occasionally lower, have been reported in patients taking tamoxifen for breast cancer. Periodic complete blood counts, including platelet counts, may be appropriate. There is evidence of an increased incidence of ischaemic cerebrovascular events and thromboembolic events, including deep vein 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 have been reported commonly with patients receiving Tamoxifen Sandoz.

Very rarely, 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).

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

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 [Adverse 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. 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 *Warnings and Precautions section*).

Overdosage

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.

Pharmaceutical precautions

Instructions for use/handling

Nil.

Incompatibilities

None known.

Special precautions for storage

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

Medicine classification

Prescription Medicine.

Package quantities

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

Further information

List of excipients

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

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