Tamoxifen "Ebewe"

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains 10mg, 20mg or 30mg tamoxifen as active ingredient.
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablets for oral administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast cancer and endometrium carcinoma in women.

As adjuvant therapy for women with positive axillary node breast cancer and also the treatment of metastatic breast cancer in men and women. Women who are oestrogen receptor positive and postmenopausal women are more likely to respond to tamoxifen. Tamoxifen may be given with chemotherapeutic agents and irradiation.

4.2 Posology and method of administration

The recommended daily dose of tamoxifen is 20mg daily. Doses of 30mg or 40mg daily have been used in patients with advanced disease.
No modification to the dosage need be made in the elderly or in patients with renal or hepatic dysfunction.

No dosage regimen has been determined for children

The maximum daily dose of tamoxifen is 40mg. An objective response is usually observed within four to ten weeks of therapy, but may take several months in patients with bone metastases.

Tablets are to be taken with some fluid.

If taking of more than one Tamoxifen "Ebewe" - tablet is necessary they can be taken once or twice a day.

Duration of treatment depends on severity of the disease, commonly long-term treatment rsp. until relapse occurs.

4.3 Contraindications

Hypersensitivity to tamoxifen or an other ingredient of the drug product.
Severe thrombocytopenia, leukopenia or hyercalcaemia.
Pregnancy.

4.4 Special warning and special precautions for use

Special caution and monitoring is to be taken to patients with:
liver- and kidney disease, diabetes mellitus, thromboembolic disease in the medical history, visual disturbances.

An increased incidence of endometrial changes, including hyperplasia, polyps and cancer, 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.
Before starting the treatment any patients receiving or having previously received tamoxifen should be given at least 6-monthly intervals gynaecological as well as internal examinations, and any unusual symptoms, abnormal vaginal bleeding, or who present with menstrual irregularities, vaginal discharge and symptoms such as pelvic pain or pressure should be investigated promptly.
Women taking tamoxifen for prophylaxis of breast cancer should be monitored carefully for endometrial hyperplasia. If atypical hyperplasia develop, tamoxifen should be discontinued while the condition is treated and a hysterectomy should be considered before tamoxifen is re-started.

Visual disturbance including decreased visual acuity, corneal opacities, cataracts and retinopathy have been described. Therefore ophthalmological examinations are recommended prior and periodical during the treatment and if visual abnormalities occur (decrease of the eyesight). The examination, may detect early corneal or retinal lesions which may be reversible on stopping treatment.

Before starting the treatment an allround gynaecologic examination (exclusion of pregnancy) as well as internal examination of the patient has to be done. During treatment gynaecologic examinations have to be done at least in 6-monthly intervals because of possible endometrium lesions and -changes.

In case of pre-existing liver diseases the liver status has to be monitored carefully. Blood count (especially thrombocytes), liver- and kidney-functions, serum calcium and blood sugar are to be controlled periodically. Further periodically controls (lung- and bone x-ray, ultrasound liver) are recommended to see possible metastasing early.

4.5 Interactions with other medicinal products and other forms of interaction

With concomitant treatment with oestrogen-containing hormone-medications a decrease of both effects is possible (e.g. unreliable effect of the "Pill").

Concomitant use of tamoxifen with coumarin-type anticoagulants may result in an increase in the anticoagulant effect (marked prolongation of prothrombin times).
Concomitant use of tamoxifen with thrombocyte aggregation inhibitors may increase the bleeding tendency during a possible thrombocytopenic phase.
A close monitoring of the coagulation status is recommended.

Thromboembolic events have been reported more frequently when tamoxifen is given in combination with cytotoxic agents.

Concomitant bromcriptine therapy has been shown to elevate serum tamoxifen and its active metabolite N-demethyl tamoxifen.

The influence of food on the absorption of tamoxifen has not been studied. However, it is unlikely to influence steady-state kinetic parameters.

4.6 Pregnancy and lactation

Tamoxifen must not be given 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.

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.

Before starting treatment pregnancy has to be excluded. Contraceptive measures have to be taken at least up to 3 months after the end of therapy. The contraceptive "Pill" is not indicated. Before starting the therapy weaning is recommended.

It is not known whether tamoxifen is distributed into breast milk. Breast feeding is not recommended during tamoxifen therapy.

4.7 Effect on ability to drive and use machines

Tamoxifen therapy is unlikely to impair driving performance or the ability to operate machines.

4.8 Undesirable effects

The most frequently reported undesirable effects are due to tamoxifen's anti-oestrogenic effect and include hot flushes, abnormal vaginal bleeding, including menstrual irregularities, vaginal discharge and pruritus vulvae. Other effects include fluid retention, nausea, vomiting and less frequently tumour flare, light-headedness, skin rash and alopecia, tiredness and headache.

In males, impotence or loss of libido.

Rarely anorexia, impairment of taste sense, obstipation, diarrhoe, convulsions of legs, depressions and alopecia or intensified hair growth.

Menstruation may be suppressed in premenopausal women.

Reversible cystic ovarian swellings have occasionally been observed in premenopausal women receiving tamoxifen.

A small number of patients with bony metastases have developed hypercalcaemia on initiation of therapy. An initial increase of bone- and tumor pain and increased erythema around skin lesions, which can be taken as an indicator for response on treatment, are possible. Enlargement of existing skin lesions or appearance of new ones is possible.

More serious undesirable effects include: leukopenia and/or thrombocytopenia (platelet counts usually between 80.000 and 90.000/mm^3) and very rarely neutropenia and pancytopenia.

Tamoxifen has been associated with an increased risk of the development of proliferative endometrial changes, as the development of endometrial hyperplasia, polyps, endometriosiss and in rare cases endometrial cancer. The risk of endometrial cancer increases with duration of therapy and have been estimated to be 2 to 3-fold greater in tamoxifen treated patients than in untreated women. But the clinical benefit in women with breast cancer outweights any increased risk of endometrial neoplasm.

Opthalmological disturbances including decreased visual acuity, corneal opacities, cataracts and retinopathy have been described. Probably these effects are depending on the dosage and the duration of treatment and may show improvement once Tamoxifen is discontinued.

Commonly thrombosis and very rarely embolism (pulmonary) have been described.

The concomitant administration of tamoxifen and cytotoxic agents may increase the risk of thromboembolic events.

Tamoxifen has an effect on serum lipid profiles, hypertriglyceridemia has been reported very rarely, partly with pancreatitis.

Tamoxifen has been associated with increases in hepatic enzymes and on rare occasions with more severe hepatic abnormalities including fatty liver, cholestasis and hepatitis.

Hypersensitivity reactions including skin rashes, angioedema, erythema multiforme, Stevens-Johnson Syndrome and bullous pemphigoids may rarely appear.

Most of these side-effects are reversible and can often be treated by dose-reduction.

4.9 Overdose

In animals high doses of tamoxifen may produce oestrogenic effects. Acute overdosage has not been reported in humans.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Tamoxifen is a potent nonsteroidal oestrogen antagonist. It also exhibits partial or full agonist properties depending on the target tissue and species studied. In humans the effect is predominantly antioestrogenic.

Tamoxifen exhibits antioestrogenic activity in humans by binding to the steroid blocking domain of the oestrogen receptor and blocking the action of oestradiol.

5.2 Pharmacokinetic properties

Tamoxifen is readily absorbed following oral administration with peak plasma concentrations measured after 4 to 7 hours and steady-state levels reached at 4 to 6 weeks. In male volunteers a single dose of tamoxifen given as a solution resulted in peak plasma concentrations of tamoxifen 42µg/l and metabolite, N-demethyl tamoxifen 12µg/l. The half-lives of the drug and metabolite were approximately 4 and 9 days, respectively. The ratio of N-demethyl tamoxifen to tamoxifen appears to increase from 20% after the first dose to around 200% at steady-state, possibly due to the longer elimination half-life of the metabolite. Following the administration of tamoxifen 20 mg b.i.d. mean steady-state levels of tamoxifen 310µg/l (164–494) and the metabolite 481µg/l (300–851) have been reported.

After administration of tamoxifen 40mg/day, tumour biopsy samples contained concentrations of tamoxifen and N-demethyl tamoxifen as follows: tamoxifen 5.4 to 117 (mean 25.1) ng/mg protein; and N-demethyl tamoxifen 7.8 to 210 (mean 52) ng/mg protein. Plasma concentrations were 27 to 520 (mean 300) ng/ml and 210 to 761 (mean 462) ng/ml. Tamoxifen appears to be greater than 99% plasma protein bound.

Tamoxifen undergoes extensive hepatic metabolism with biliary excretion being the main route of elimination in humans. Urinary elimination of unchanged drug is negligible. Demethylation to the active metabolite N-demethyl tamoxifen is the principal metabolic pathway in humans, with further N-demethylation to the N-dedimethyl metabolite. Elimination of tamoxifen appears to be biphasic, with an initial phase of about 7 to 14 hours in female patients, and a terminal phase ($t_{1/2}$) of around 7 days. The elimination half-life of the N-demethyl metabolite appears to be 14 days.

Tamoxifen plasma levels ≥70µg/l were associated with clinical response.

The pharmacokinetics of tamoxifen and its main metabolites do not appear to have been studied in the elderly, in patients with hepatic dysfunction or in the fed and fasted state.

5.3 Preclinical safety data

In rats tamoxifen at doses of 5, 20 and 35mg/kg per day for up to two years produced a dose-related incidence of hepatocellular carcinoma. Independent reports of six month studies in rats revealed malignant liver tumours. In a 13 month study of endocrine changes in immature and mature mice, granulosa cell ovarian tumour and interstitial cell testicular tumours were found in tamoxifen treated mice but not the controls. No genotoxicity potential was found.

In rodent models of foetal reproductive tract development, at doses 0.3 to 2.4 times the maximum human recommended dose, tamoxifen caused changes in both sexes that were similar to those caused by oestradiol and diethylstilboestrol: vaginal adenosis similar to those found in young women who were exposed in utero to diethylstilboestrol and had a 1 in 1000 risk of developing clear-cell adenocarcinoma of the vagina or cervix.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, microcrystalline cellulose, maize starch, colloidal silicon dioxide, magnesium stearate.

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C.

Store in dry conditions. Keep container in the outer carton, in order to protect from light.

6.5 Nature and contents of container

Polypropylene bottle with a polyethylene stopper.

30 tablets containing 10mg of tamoxifen, each.
30 tablets containing 20mg of tamoxifen, each.
30 tablets containing 30mg of tamoxifen, each.

6.6 Instructions for use and handling

None.

7. MANUFACTURER

EBEWE Pharma Ges.m.b.H. Nfg. KG
A-4866 Unterach, AUSTRIA

8. DATE OF (PARTIAL) REVISION OF THE TEXT

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Ebewe PHARMA