SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Mamofen 10 (Tamoxifen Tablets BP 10 mg)

2. Pharmaceutical Form

Pharmaceutical Dosage form of the product: Tablet

Strength : 10 mg

Route(s) of administration: Oral route of administration

3. Qualitative and Quantitative Composition

Each uncoated tablet contains:
Tamoxifen Citrate BP
Equivalent to Tamoxifen ..... 10 mg

4. Clinical Particulars

Therapeutic indications

i) Indicated for the treatment of breast carcinoma, particularly in oestrogen receptor positive patients.
ii) For the treatment of anovulatory infertility.

Posology and method of administration

Breast carcinoma: 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 30-40mg per day is not available although these doses have been used in some patients with advanced disease.
Elderly patients: Similar dosage regimens of tamoxifen have been used in elderly patients with breast cancer and in some of these pateints it has been used as sole therapy.
Anovulatory infertility: Before commencing any course of treatment, whether initial or subsequent, the possibility of pregnancy must be excluded. In women with regular menstruation but anovular cycles, treatment should be initiated with 20mg daily given on the second, third, fourth and fifth days of the menstrual cycle. If treatment is unsuccessful (unsatisfactory basal temperature records or poor pre-ovulatory cervical mucus), further courses may be given during subsequent menstrual periods, increasing the dosage to 40mg and then 80mg daily.
In women with irregular menstruation, treatment may be initiated on any day. If no signs of ovulation are apparent, a subsequent course of treatment may be commenced 45 days later with dosage increased as above. If the patient responds with menstruation, the next course of treatment should start on the second day of

the cycle.

Method of administration
Oral Route of Administration

Contraindications
Tamoxifen is contraindicated in patients with known hypersensitivity to the drug or any of its ingredients.
Tamoxifen must not be administered during pregnancy. Pre-menopausal women must be carefully examined to exclude the possibility of pregnancy before commencement of treatment for breast carcinoma or infertility.

Special warning & precautions for use
Effects in Metastatic Breast Cancer Patients: If hypercalcemia occurs within a few weeks of starting treatment with Mamofen, appropriate measures should be taken and, if severe, Mamofen should be discontinued.
Effects on the Uterus-Endometrial Cancer and Uterine Sarcoma: An increased incidence of uterine malignancies has been reported in association with

tamoxifen treatment. The underlying mechanism is unknown, but may be related to the estrogen-like effect of tamoxifen. Most uterine malignancies seen in association with tamoxifen are classified as adenocarcinoma of the endometrium. Any patient receiving or who has previously received tamoxifen who reports abnormal vaginal bleeding should be promptly evaluated. Patients receiving or who have previously received tamoxifen should have annual gynecological examinations and they should promptly inform their physicians if they experience any abnormal gynecological symptoms, eg, menstrual irregularities, abnormal vaginal bleeding, changes in vaginal discharge, or pelvic pain or pressure.

There are no data to suggest that routine endometrial sampling in asymptomatic women taking tamoxifen to reduce the incidence of breast cancer would be beneficial.

Thromboembolic Effects of tamoxifen: There is evidence of an increased incidence of thromboembolic events, including deep vein thrombosis and pulmonary embolism, during tamoxifen therapy. When tamoxifen is coadministered 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 should be carefully considered in women with a history of thromboembolic events.

Effects on the Eye: Ocular disturbances, including corneal changes, decrement in color vision perception, retinal vein thrombosis, and retinopathy have been reported in patients receiving tamoxifen. An increased incidence of cataracts and the need for cataract surgery have been reported in patients receiving tamoxifen.

Pregnancy Category D: Tamoxifen may cause fetal harm when administered to a pregnant woman. Women should be advised not to become pregnant while taking tamoxifen or within 2 months of discontinuing tamoxifen and should use barrier or nonhormonal contraceptive measures if sexually active.

There are no adequate and well-controlled trials of tamoxifen in pregnant women. There have been a small number of reports of vaginal bleeding, spontaneous abortions, birth defects, and fetal deaths in pregnant women. If this drug is used during pregnancy, or the patient becomes pregnant while taking this drug, or within approximately two months after discontinuing therapy, the patient should be apprised of the potential risks to the fetus including the potential long-term risk of a DES-like syndrome.

PRECAUTIONS

General: Decreases in platelet counts, usually to 50,000-100,000/mm^3, infrequently lower, have been occasionally reported in patients taking tamoxifen for breast cancer. In patients with significant thrombocytopenia, rare hemorrhagic episodes have occurred, but it is uncertain if these episodes are due to tamoxifen therapy. Leukopenia has been observed, sometimes in association with anemia and/or thrombocytopenia. There have been rare reports of neutropenia and pancytopenia in patients receiving tamoxifen; this can sometimes be severe.

Reduction in Invasive Breast Cancer and DCIS in Women with DCIS: Women with DCIS treated with lumpectomy and radiation therapy who are considering tamoxifen to reduce the incidence of a second breast cancer event should assess the risks and benefits of therapy, since treatment with tamoxifen decreased the incidence of invasive breast cancer, but has not been shown to affect survival.

Reduction in Breast Cancer Incidence in High Risk Women: Women who are at high risk for breast cancer can consider taking tamoxifen therapy to reduce the incidence of breast cancer. Whether the benefits of treatment are considered to outweigh the risks depends on a woman's personal health history and on how she weighs the benefits and risks. Tamoxifen therapy to reduce the incidence of breast cancer may therefore not be appropriate for all women at high risk for breast cancer. Women who are considering tamoxifen therapy should consult their health care professional for an assessment of the potential benefits and risks prior to starting therapy for reduction in breast cancer incidence.

Women who are pregnant or who plan to become pregnant should not take tamoxifen to reduce her risk of breast cancer. Effective nonhormonal contraception must be used by all premenopausal women taking tamoxifen and for approximately two months after discontinuing therapy if they are sexually active.

Monitoring During Tamoxifen Therapy: Women taking or having previously taken tamoxifen should be instructed to seek prompt medical attention for new breast lumps, vaginal bleeding, gynecologic symptoms (menstrual irregularities, changes in vaginal discharge, or pelvic pain or pressure), symptoms of leg swelling or tenderness, unexplained shortness of breath, or changes in vision. Women should inform all care providers, regardless of the reason for evaluation, that they take tamoxifen.

Women taking tamoxifen to reduce the incidence of breast cancer should have a breast examination, a mammogram, and a gynecologic examination prior to the initiation of therapy. These studies should be repeated at regular intervals while on therapy, in keeping with good medical practice.

Laboratory Tests: Periodic complete blood counts, including platelet counts and periodic liver function tests should be obtained.

Pregnancy Category D: See **WARNINGS**.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from tamoxifen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and efficacy of tamoxifen for girls aged two to 10 years with McCune-Albright Syndrome and precocious puberty have not been studied beyond one year of treatment. The long-term effects of tamoxifen therapy for girls have not been established.

Geriatric Use: No overall differences in tolerability were observed between older and younger patients.

Interaction with other medicinal prodcuts 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 coadministration exists, careful monitoring of the patient's prothrombin time is recommended.

There is an increased risk of thromboembolic events occurring when cytotoxic agents are used in combination with tamoxifen.

Tamoxifen reduced letrozole plasma concentrations by 37%. The effect of tamoxifen on metabolism and excretion of other antineoplastic drugs, such as cyclophosphamide and other drugs that require mixed function oxidases for activation is not known. Tamoxifen and N-desmethyl tamoxifen plasma concentrations have been shown to be reduced when coadministered with rifampin or aminoglutethimide. Induction of CYP3A4-mediated metabolism is considered to be the mechanism by which these reductions occur; other CYP3A4 inducing agents have not been studied to confirm this effect. One patient receiving tamoxifen with concomitant phenobarbital exhibited a steady state serum level of tamoxifen lower than that observed for other patients (ie, 26 ng/mL vs. mean value of 122 ng/mL). However, the clinical significance of this finding is not known. Rifampin induced the metabolism of tamoxifen and significantly reduced the plasma concentrations of tamoxifen in 10 patients. Aminoglutethimide reduces tamoxifen and N-desmethyl tamoxifen plasma concentrations. Medroxyprogesterone reduces plasma concentrations of N-desmethyl, but not tamoxifen.

Concomitant bromocriptine therapy has been shown to elevate serum tamoxifen and N-desmethyl tamoxifen.

Pregnancy and lactation

Pregnancy: Tamoxifen may cause fetal harm when administered to a pregnant woman. Women should be advised not to become pregnant while taking tamoxifen or within 2 months of discontinuing tamoxifen and should use barrier or nonhormonal contraceptive measures if sexually active.

There are no adequate and well-controlled trials of tamoxifen in pregnant women. There have been a small number of reports of vaginal bleeding, spontaneous abortions, birth defects, and fetal deaths in pregnant women. If this drug is used during pregnancy or the patient becomes pregnant while taking this drug, or within approximately two months after discontinuing therapy, the patient should be apprised of the potential risks to the fetus including the potential long-term risk of a DES-like syndrome.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from tamoxifen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Effects on ability to drive and use machine

Not known.

Undesirable effects

Side effects are generally mild. Hot flushes, mild nausea, mild thrombocytopenia and leucopenia have been reported.

Pruritus vulvae, skin rash, alopecia, fluid retention, gut tenderness, gastrointestinal pain, pain from metastases and tumour pain have occasionally occurred.

An increased incidence of endometrial hyperplasia, endometrial polyps and endometrial carcinoma have been reported in association with tamoxifen treatment.

Abnormal vaginal bleeding including menstrual irregularities, vaginal discharge and symptoms such as pelvic pain or pressure in patients who are receiving or have previously received tamoxifen should be promptly investigated.

There have been infrequent reports of thromboembolic events occurring during tamoxifen therapy. As an increased incidence of these events is known to occur in patients with malignant disease, a causal relationship with tamoxifen has not been established.

A number of cases of visual disturbance including corneal changes, cataracts and retinopathy, have been described in patients receiving tamoxifen therapy.

Transient falls in platelet count (usually only 80,000-90,000 per cu mm but occasionally lower), have been reported in patients receiving tamoxifen for breast carcinoma. Platelet counts have recovered during treatment and no haemorrhagic tendency has been reported.

Hypercalcaemia has been reported in patients with bone metastases.

Menstruation may be suppressed in a proportion of pre-menopausal women receiving treatment for breast carcinoma; reversible cystic ovarian swelling has occasionally been observed in this group of patients receiving 40mg of tamoxifen twice daily for short periods.

Significant increases in anticoagulant effect may occur if tamoxifen is used in combination with coumarin type anticoagulants (eg warfarin). Careful monitoring of patients is recommended if co-administration is initiated.

Tamoxifen has been associated with changes in liver enzyme levels and rarely with more severe liver abnormalities including fatty liver, cholestasis and hepatitis.

When side-effects are severe it may be possible to control them by a simple reduction of dosage without loss of control of the disease. If side-effects do not respond to this measure, it may be necessary to stop treatment.

Overdose

Signs observed at the highest doses following studies to determine LD_{50} in animals were respiratory difficulties and convulsions. Acute overdosage in humans has not been reported.

No specific treatment for overdosage is known; treatment must be symptomatic.

5. Pharmacological Properties

Pharmacodynamic Properties

Pharmacotherapeutic group: Antineoplastic

ATC code: L02BA01

Clinical Pharmacology:

Tamoxifen is a nonsteroidal agent that has demonstrated potent antiestrogenic properties in animal test systems. The antiestrogenic effects may be related to its ability to compete with estrogen for binding sites in target tissues such as breast. Tamoxifen inhibits the induction of rat mammary carcinoma induced by dimethylbenzanthracene (DMBA) and causes the regression of already established DMBA-induced tumors. In this rat model, tamoxifen appears to exert its antitumor effects by binding the estrogen receptors.
In cytosols derived from human breast adenocarcinomas, tamoxifen competes with estradiol for estrogen receptor protein.

Pharmacokinetic Properties

Absorption and Distribution - Following a single oral dose of 20 mg tamoxifen, an average peak plasma concentration of 40 ng/mL (range 35 to 45 ng/mL) occurred approximately 5 hours after dosing. The decline in plasma concentrations of tamoxifen is biphasic with a terminal elimination half-life of about 5 to 7 days. The average peak plasma concentration of N-desmethyl tamoxifen is 15 ng/mL (range 10 to 20 ng/mL). Chronic administration of 10 mg tamoxifen given twice daily for 3 months to patients results in average steady-state plasma concentrations of 120 ng/mL (range 67-183 ng/mL) for tamoxifen and 336 ng/mL (range 148-654 ng/mL) for N-desmethyl tamoxifen. The average steady-state plasma concentrations of tamoxifen and N-desmethyl tamoxifen after administration of 20 mg tamoxifen once daily for 3 months are 122 ng/mL (range 71-183 ng/mL) and 353 ng/mL (range 152-706 ng/mL), respectively. After initiation of therapy, steady state concentrations for tamoxifen are achieved in about 4 weeks and steady-state concentrations for N-desmethyl tamoxifen are achieved in about 8 weeks, suggesting a half-life of approximately 14 days for this metabolite. In a steady-state, crossover study of 10 mg Tamoxifen tablets given twice a day vs. a 20 mg Tamoxifen tablet given once daily, the 20 mg Tamoxifen tablet was bioequivalent to the 10 mg Tamoxifen tablets.
Metabolism - Tamoxifen is extensively metabolized after oral administration. N-desmethyl tamoxifen is the major metabolite found in patients' plasma.
The biological activity of N-desmethyl tamoxifen appears to be similar to that of tamoxifen. 4-Hydroxytamoxifen and a side chain primary alcohol derivative of tamoxifen have been identified as minor metabolites in plasma. Tamoxifen is

a substrate of cytochrome P-450 3A, 2C9 and 2D6, and an inhibitor of P-glycoprotein.

Excretion - Studies in women receiving 20 mg of ^{14}C tamoxifen have shown that approximately 65% of the administered dose was excreted from the body over a period of 2 weeks with fecal excretion as the primary route of elimination. The drug is excreted mainly as polar conjugates, with unchanged drug and unconjugated metabolites accounting for less than 30% of the total fecal radioactivity.

Special Populations - The effects of age, gender and race on the pharmacokinetics of tamoxifen have not been determined. The effects of reduced liver function on the metabolism and pharmacokinetics of tamoxifen have not been determined.

6. Pharmaceutical Particulars

6.1 List of Excipients

Microcrystalline Cellulose BP (Avicel pH 112)
Croscarmellose Sodium (Ac-Di-Sol) USPNF
Colloidal Anhydrous Silica BP
Magnesium Stearate BP

6.2 Incompatibilities

None

6.3 Shelf life

The shelf life of the medicinal product as package for sale
48 Months

The shelf life after dilution or reconstitution according to directions
Not Applicable.

The shelf life after first opening the container
Not Applicable

6.4 Special precaution for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

UNIT PACK: 10 tablets in strip. Such 10 strips packed in a printed carton along with the pack insert.

7. Marketing Authorization Holder and Manufacturing site address

Name of Marketing Authorization Holder:
Khandelwal Laboratories Pvt. Ltd.

Address of manufacturing site:
B-1, Wagle Industrial Estate,
Thane - 400 604, India
Telephone: 00 91 22 25821793 / 0794
Fax: 00 91 22 25823837

8. Marketing Authorization Numbers

04409/3380/NMR/2017

9. Date of first authorization / renewal of the authorization

Apr 15, 2019

10. Date of revision of the text
