TAMOX TABLETS

(Tamoxifen Citrate U.S.P.)

Antiestrogin Antineoplastic

10 ملی گرام

ٹے موکس 20 ملی گرام گولیاں

(ٹے موکسی فین) یو۔ایس۔پی

Composition:

Each film coated tablet contains : Tamoxifen 10mg as Tamoxifen citrate U.S.P.
Each film coated tablet contains : Tamoxifen 20mg as Tamoxifen citrate U.S.P.
(Product complies U.S.P. specification)

Action And Clinical Pharmacology : Tamoxifin is a nonsteroidal agent which has demonstrated potent antiestrogenic properties in animal test systems. The antiestrogenic effects are related to is ability to complete with estrogen for binding sites in target tissues such as breast and uterus. Tamoxifen inhibits the induction of ratmammary carcinoma induced by dimethylbe-nzanthracene (DMBA) and causes the regression of already established DMBA-inducrd tumors. In this rat model tamoxifen appears to exerts its antitumor effects by binding estrogen receptors.

In cytosols derived from human endometrium and human breast and uterine adenocarcinomas tamoxifin competes with estradiol for estrogen receptor protein.

Reports of advanced breast cancer trials conducted world-wide, however, indicate that, using established criteria, there is an objective response rate (complete and partial remission) to tamoxifen of approximately 10% in patients with estrogen receptor negative tumors which may indicate other mechanisms of action. A further small percentage of patients show positive benifit in that they are reported to have disease stabilization. This may be explained by the shortcomings of the assay procedure or by actions of tamoxifen at loci other than the estrogen receptor.

Ranges as large a 0 to 300 fmoL/mg protein have been reported in histographically comparable portions of the same tumor. In addition, the collection, transport and storage of tumor specimenes can affect the validity of current estorage receptor assays. The apparent discrepancy in correlation between estrogen receptor status and clinical response may also be explained by recent in vitro evidence indicating that not all of the growth inhibiting effects of tamoxifen are mediated through the estrogen receptor. Tamoxifen has been shown to have low affinity for the androgen receptor and on a binding site distinct from the androgen receptor and on a binding site distinct from the estrogen receptor. The possibility also exists that tamoxifen interferes with the action of hormonal steroids on cell growth, that it could modulate the action of peptide hormones at their receptors by effects on cell membranes, and that it inhibits prostaglandin synthetase thereby having the potential to limit tumor growth.

It is recognized that tamoxifen also displays estrogenic- like effects on several body systems including the endometrium, bone and blood lipids.

Therefor, although evidence suggests that patients with estrogen receptor positive tumors are more likely to respond, tamoxifen therapy may be considered in patients whose estrogen receptor status is unknown, in doubt or negative.

Indications And Uses: The treatment of breast cancer in estrogen receptor positive tumors.

Contra-Indications: Pregnancy: Tamoxifen must not be given 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.

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

In rodent models of fetal reproductive tract development, tamoxifen was associated with changes similar to those caused by estradiol, ethynylestradiol, clomiphene and diethylstiboetrol (DES). Although the clinical relevance of these changes is un-known, some of them, specially vaginal adenosis, are similar to those seen in young women who were exposed to DES in utero and who have a 1 and 1000 risk of developing clear-cell carcinoma of all the vagina and cervix. Only a small number of pregnant woman have been exposed to tamoxifin. 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 tamoxifin. Women should be advised not to become pregnant while taking tamoxifen and should use barrier or either nonbormonal contraceptive methods if sexually active. Pre-monopause patients must be carefully examined before treatment to exclude the possibility of pregnancy. Women should be apppraised of the potential risks to the fetus, should the become pregnant while tamoxifen or within 2 months of cessation of therapy.

Manufacturer's Warnings in Clinical States: In rats tamoxifen can induce preneoplastic and neoplastic changes of the liver including hepatocellular carcinomas when administered at high doses for prolonged periods. In that species tamoxifen behaves as a partial agonist where as it is primarily an antiastrogen in humans. For this reason and considering the high dosage used in the rat studies(up to 100 times the normal human therapeutic dose), the relevance of these findings to human use is unknown.

Gonadal tumors have been reported in mice receiving tamoxifen. To date, no case of hepatocellular carcinoma has been reported in patients receiving tamoxifen. However, the possibility of potential carcinogenicity in human should be considered.

Cataracts have also been found in chronic toxcity studies in rats. Tests conducted in various in vitro and in vivo systems have demonstrated that tamoxifen possesses genotoxic potential following hepatic metabolism. The significance of these result for man is at unclear. A number of second primary tumors, occuring at sites other than the endometrium and the opposite breast, have been reported in patients receiving tamoxifen. However, the possibilty of potential carcinogenicity in humans should be considered. Cataracts have also been found in chronic toxicity studies in rats. Tests conducted in various in vitro and in vivo systems have demonstrated that tamoxifen possesses genotoxic potential following hepatic metabolism. The significance of these results for man is at present unclear.

A number of second primary tumors, occuring 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 casual link has been established and the clinical significance of these observations remains unclear.

Precautions: Use tamoxifen cautiously in patients with existing thrombocytopenia or leukopenia. Transient decreases in platelet counts usually to 50,000 to 1000,000/mm, have been observed occasionally during treatment. However, no hemorrhagic tendency was reported and platelet counts returned to normal even through treatment was continued.

Transient decreases in leukocytes also have been observed occasionally during treatment. Although it was uncertain that these incidences of leukopenia and thrombocytopenia were due to tamoxifen therapy, complete blood counts, including platelet counts, should be obtained periodically. As with other additive hormonal therapy (estrogen and androgens) hypercalcemia has been reported in some breast cancer patients with bone metartases within a few weeks of starting treatment with temoxifen.

Patient who have metastatic bone disease should have periodic serum calcium determinations during the first few weeks of tamoxifen therapy and any symptoms suggestive of hypercalcemia should be evaluated promptly. If hypercalcemia is present, appropriate measure should be evaluated promptly. If hypercalcemia is present, appropriate measure should be taken, and if severe, tamoxifen should be discontinued.The first patient follow-up should be done within 1 month following initiation of treatment. Thereafter, examinations may be performed at 1 to 2- months intervals. If adverse reactions such as hot flashes, nausea or vomiting occur, and severe, they may be controlled in some patients by a dosage reduction without loss of effect on the disease. Bone pain, if it should occur, may require analgesics.

Any patients receiving tamoxifen or having previously received tamoxifen who report abnormal vaginal bleeding should be promptly investigated.

In clinical studies, the median duration of treatment before the onset of a definite objective response has been 2 month. However, approximately 25% of patients who eventually responded were treated for 4 or more months before a definite response was recorded.

The duration of tamoxifen treatment will depend on the patient's response. The drug should be continued as long as there is a favorable response.

With obvious disease progression, discontinue tamoxifen. However, because an occasional patient will have a local disease flare or an increase in bone pain shortly after starting tamoxifen, it is sometime difficult during the first few weeks of treatment to determine whether the patient's disease is progressing or whether it will stabilize or response to continued treatment. There are data to suggest that, if possible, treatment should not be discontinued before a minimum of 3 to 4 weeks.

Drug Interactions: When tamoxifen is used in combination with cytotoxic agents, there is increased risk of thromboembolic events occurring.

Adverse Reactions: The most frequent adverse reactions to tamoxifen are hot flushes, nausea and vomiting. These may occur in up to 25% of patients and are rarely severe enough to require discontinuation of treatment.

Less frequently reported adverse reactions are vaginal bleeding, vaginal discharge and skin rash. Usually these have not been severe enough to require dosage reduction or discontinuation of treatment.

Increased bone and tumor pain and also local disease flare have occurred. These are sometimes associated with good tumor response. Patients with soft tissue disease may marked erythema within and surrounding the lesions, and/or the development of new lesions. When they occur, the bone pain or disease flare are seen shortly after starting tamoxifen and generally subside rapidly.

Ocular changes have been reported in a few patients treated for periods longer than 1 year with doses that were at least 4 times the highest recommended daily dose of 40 mg. The ocular changes consisted of retinopathy and in a few patients, there were also corneal changes and decreased visual acuity. There were multiple light refractive opacities in the paramacular area, andmacular edema. The corneal lesions consisted of whorl-like superficial opacities. Ophthalmological examinations of selected patients on long-term tamoxifen therapy in the recommended doses revealed no ocular pathology attributable to the drug.

In addition, a few cases of ocular changes including visual disturbance, cataracts, and/or corneal changes and/or retinopathy have been reported in patients treated with tamoxifen at recommended doses. It is uncertain if these effects are due to the drugs.

Leukopenia has been observed following the administration of tamoxifen, sometimes in association with anemia and/or thrombocytopenia. Neutropenia has been reported on rare occasions; this canm sometimes be severe.

Elevations of ALT , AST and GGT levels have been reported on rare occasions in association with tamoxifen therapy. The incidence of overt cholestasis appears to be very low (<1%) but it should be kept in mind while administering tamoxifen over the long-term.

There have been infrequent reports of thromboembolic events occuring 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.

Other adverse reactions noted infrequently are hypercalcemia, peripheral edema, benign symptomatic hepatic cysts, peliosis hepatitis, distaste for food, pruritus vulvae, depression, dizziness, lightheadedness and headache.

Tamoxifen therapy has been associated with an increased incidence of endometrial carcinoma. Uterine fibroids have been reported.

Symptoms And Treatment Of Overdose: Symptoms: Acute overdosage in humans has not been reported. Possible overdosage effects might include hot flushes, nausea, vomiting and vaginal bleeding.

Treatment: Symptomatic treatment. In the case of childhood accidental ingestion, gastric emptying is suggested.

Dosage And administration: The usual dose is 20 to 40 mg/day in a single or 2 divided doses. Use the lowest effective does.

Presentation

Tamox-10: Pack of 30 tablets in blisters.
Tamox-20: Pack of 30 tablets in blisters.

Dosage : As directed by the physician.

Instructions : Store at controlled room temperature below 25°C.
Protect from heat, light and moisture.
Keep all medicines out of the reach of children.
To be sold on prescription of registered medical practitioner only.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: 25 ڈگری سینٹی گریڈ سے کم کمرے کے درجہ حرارت پر محفوظ کریں۔

گرمی، روشنی اور نمی سے بچائیں۔ تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by :

PHARMEDIC LABORATORIES (PVT) LIMITED.

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