For the use only of a Registered Medical Practioner or a Hospital or a Laboratory

Zutam ™

TAMOXIFEN CITRATE IP TABLETS

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Composition

Tamoxifen Citrate Tablets IP 10mg

Each uncoated tablet contains

Tamoxifen Citrate IP

Equivalent to Tamoxifen.....10mg

Tamoxifen Citrate Tablets IP 20mg

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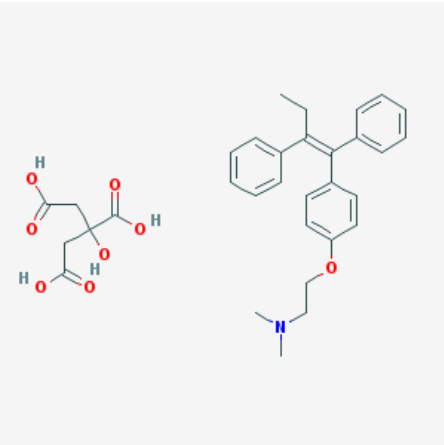
Tamoxifen Citrate IP

Equivalent to Tamoxifen 20mg

Description

Tamoxifen, a nonsteroidal antiestrogen, is a triphenylethylene derivative with both estrogen antagonist on breast tissue and in the CNS and as an estrogen agonist on endometrium, bone and lipids.

Tamoxifen and at least several of its metabolites compete with estradiol for binding to cytyplasmic estrogen receptors in tissues such as breast, uterus, vagina, anterior pituitary, and tumors containing high concentrations of estrogen receptors.



PHARMACOLOGH

Pharmacodynamics

Tamoxifen citrate 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 hy dimethylbenzathracene (DMBA) and causes the regression of already established DMBA-induce tumors. In this rat model, Tamoxifen appears to exert its antitumor effects by ninding the estrogen receptors.

In cytosols derived from human breast adenocarcinoma, Tamoxifen competes with estradiol for estrogen receptor protein.

Pharmacokinetics

Absorption and Distribution

Following a single oral dose of 20mg Tamoxifen, an average peak plasma concentration of 40ng/ml (range 35 to 45ng/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). Chronic administration of 10mg tamoxifen given twice daily for 3 months to patients results in average steady-state plasma concentrations of 120 ng/ml (range 71-183 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 4 weeks, suggesting a half-life of approximately 14 days for this metabolite. In a steady-state, crossover study of 10mg Tamoxifen citrated tablets given twice a day vs. a 20mg Tamoxifen citrate tablet given once daily, the 20mg Tamoxifen citrate tablet was bioequivalent to the 10 mg Tamoxifen citrate 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 14C 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.

Indications

Tamoxifen is used alone as an adjunct to surgery and radiation therapy for the treatment of breast cancer in women with negative axilliary lymph nodes and in postmenopausal women with positive axillary lymph nodes. Adjuvant Tamoxifen therapy reduces the occurrence of contralateral breast cancer in premenopausal or postmenopausal women with breast cancer.

Tamoxifen has been used to stimulate ovulation in appropriately selected an ovulatory women desiring pregnancy, especially in those with oligomenorrhea or amenorrhea who were previously receiving oral contraceptives.

Limited data also suggest that an occasional patient with malignant carcinoid tumor and carcinoid syndrome may have a beneficial response to Tamoxifen.

Dosage and Administration

Tamoxifen is administered orally.

Breast cancer

Adjuvant therapy

When Tamoxifen is used alone as an adjunct to surgery and radiation therapy in the treatment of breast cancer, the usual dosage of the drug is 20-40 mg daily. Dosages exceeding 20 mg daily should be given in divided doses (morning and evening). There is no evidence that higher dosages are necessary. The optimum duration of adjuvant Tamoxifen therapy has not been established, but therapy for about 5 years is more effective than shorter courses of therapy. Longer therapy (i.e. beyond 5 years) with Tamoxifen is not recommended for routine use in women with node-negative breast cancer.

When Tamoxifen is use in combination with chemotherapy as an adjunct to surgery in the treatement of breast cancer in postmenopausal women or in women 50 years of age or older who have positive axillary lymph nodes, the usual dosage of the drug is 10 mg twice daily. The optimum duration of adjuvant Tamoxifen therapy has not been established.

Metastatic Breast Cancer

For the treatment of metastatic breast cancer in women, the usual dosage of Tamoxifen is 20-40 mg daily. Dosages exceeding 20 mg daily should be given in divided doses (morning and evening). Because there does not appear to be any significant difference in response rates with the two dosages, most clinicians believe that 20 mg daily usually should be used initially. If an objective response to the drug occurs, it usually is evident within 4-10 weeks; however, several months of therapy may be required before an objective response occurs in patients with bone metastases.

Reduction in the incidence of breast cancer in women at high risk

For reduction in the incidence of breast cancer in women at high risk, the recommended dosage of Tamoxifen is 20 mg daily. Because of negative findings and a lack of additional benefit associated with more prolonged therapy with drug as an adjuvant in the treatment of breast cancer, a 5-year duration of Tamoxifen therapy currently is being recommended for the prevention of breast cancer in women at high risk of the disease.

Male Breast Cancer

For the treatment of advanced (metastatic) breast cancer in men, the usual dosage of Tamoxifen is 20-40 mg daily. Dosages exceeding 20 mg daily should be given in divided doses (morning and evening). When Tamoxifen alone or in combination with radiation therapy was used as an adjunct to surgery in the treatment of breast cancer in men, a Tamoxifen dosage of 20mg daily was used, usually for 1-2 years. The optimum duration of adjuvant Tamoxifen therapy has not been established; however, since adjuvant therapy of about 5 years appears to be more effective than shorter courses of therapy in women with breast cancer, some clinicians suggest the same prolonged Tamoxifen course for male patients.

Other uses

To stimulate ovulation, 5-40 mg of Tamoxifen has been administered twice daily for 4 days.

Warnings

Anticoagulants

Tamoxifen has been reported to potentiate the hypoprothrombinemia effect of warfarin. If the drugs are used concomitantly, the patient and prothrombin time should be monitored closely and dosage of the anticoagulant adjusted accordingly.

Other Drugs

Tamoxifen, N-desmethyl Tamoxifen, 4-hydroxy Tamoxifen have been found to the potent inhibitors of hepatic cytochrome P-450 mixed function oxidases. An increased risk of thromboembolic events has been observed in patients receiving Tamoxifen concomitantly with cytotoxic drugs.

Precautions

Pregnancy

Women who are pregnant or who plan to become pregnant should not use Tamoxifen to reduce the risk of breast cancer.

Nursing mother

It is not known if Tamoxifen is distributed into milk. Because of the potential for serious adverse reactions to Tamoxifen in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman.

Pediatric use

Safety and efficacy of Tamoxifen in pediatric patients have not been established.

Adverse Reactions:

Cardiovascular: Adverse cardiovascular effects of Tamoxifen include thrombotic and venous thromboembolic events such as stroke, pulmonary embolism, and deep-vein thrombosis.

Genitourinary: Vaginal discharge and menstrual irregularities, loss of libido and impotence.

Musculoskeletal: Musculoskeletal pain, bone pain and hypercalcemia. If hypercalcemia is severe, the drug should be discontinued.

Hepatic: Changes in hepatic enzyme concentrations (e.g. increased serum AST [SGOT] or ALT [SGPT] concentrations) and increased bilirubin and/or alkaline phosphatase concentrations have been reported in patients receiving Tamoxifen therapy.

GI: Adverse GI effects of Tamoxifen, including nausea, anorexia, distaste for food and abdominal cramps, have been reported in patients with breast cancer.

Nervous System: Dizziness, lightheadedness, headache, fatigue and mental depression.

Hematologic: Thrombocytopenia (platelet counts of 50,000-100,000/mm3 and, infrequently, lower) occasionally has occurred in patients receiving Tamoxifen for the treatment of breast cancer; however, platelet counts returned to normal even though Tamoxifen therapy was continued. Hemorrhagic episodes have occurred rarely in patients with severe thrombocytopenia. Neutropenia, pancytopenia, and leukopenia (white blood cell count less than 3000/mm3), sometimes associated with anemia and/or thrombocytopenia, also have been reported and may be severe.

Dermatologic: Erythema multiform, Stevens-Johnson syndrome, and bullous pemphigoid

Other Adverse Effects

Weightloss, fatigue and cough.

Drug Interactions

Do not start, stop, or change the dosage of any medicine before checking with your doctor or pharmacist first.

This drug should not be used with the following medications because very serious interactions may occur: anastrozole, letrozole.

If you are currently using any of these medications listed above, tell your doctor or pharmacist before starting tamoxifen.

Overdosage:

Symptoms of overdose may include: shaking, unsteady walking, fainting, irregular heartbeat.

Contraindications

Tamoxifen is contraindicated in women with a history of deep-vein thrombosis or pulmonary embolism and in patients with known hypersensitivity to the drug.

Storage

Store in cool, dry place.

Protect from light.

Presentation

Zutam 10mg as carton containing 10 strip of 10 tablets

Zutam 20 mg as carton containing 10 strip of 10 tablets

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TAMOXIFEN CITRATE IP TABLETS

Manufactured in India:

Zuvius Lifesciences Pvt. Ltd.

B/111-113, Kanara Business Centre, Link Road,

Laxmi Nagar, Ghatkopar (E), Mumbai – 400075.

At: B-1, Wagle Industrial Estate, Thane – 400604.

TM: Trademark Under Registration

www.zuviuslifesciences.in

Manufactured in India by:

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