Tamoxifen Hexal®

Registration Number:
P N011849/01

Trade Name of the Drug:
Tamoxifen Hexal

International Nonproprietary Name (INN):
Tamoxifen

Dosage Form:
Tablets, film-coated

Composition:
1 tablet contains:
Active Substance: Tamoxifen citrate 15.2 mg or 30.4 mg or 45.6 mg or 60.8 mg, equivalent to 10 mg, 20 mg, 30 mg or 40 mg of tamoxifen respectively.
Excipients: Lactose $1H_2O$ 71.3 mg or 142.6 mg or 213.9 mg or 285.2 mg; sodium starch glycolate 10.0 mg or 20.0 mg or 30.0 mg or 40.0 mg; povidone 2.5 mg or 5.0 mg or 7.5 mg or 10.0 mg; microcrystalline cellulose 24.8 mg or 49.6 mg or 74.4 mg or 99.2 mg; magnesium stearate 1.2 mg or 2.4 mg or 3.6 mg or 4.8 mg.
Coating: White Opadry coating 2.5 mg or 5.0 mg or 7.5 mg or 10.0 mg, consisting of: lactose 0.9 mg or 1.8 mg or 2.7 mg or 3.6 mg, titanium dioxide 0.65 mg or 1.3 mg or 1.95 mg or 2.6 mg, hypromellose 0.7 mg or 1.4 mg or 2.1 mg or 2.8 mg, PEG 4000 0.25 mg or 0.5 mg or 0.75 mg or 1.0 mg.

Description:
10 mg Tablets: Film-coated tablets, round, white or slightly yellowish, biconvex, with a uniform smooth surface.
20 mg Tablets: Film-coated tablets, round, white or slightly yellowish with a score on one side, biconvex, with a uniform smooth surface.
30 mg Tablets: Film-coated tablets, round, biconvex, white or slightly yellowish with a uniform smooth surface.
40 mg Tablets: Film-coated tablets, round, biconvex, white or slightly yellowish with a score on one side, with a uniform smooth surface.

Pharmacotherapeutic Group:
Antineoplastic agent – antiestrogen

ATC Code:
L02BA01

Pharmacological Properties:

Pharmacodynamics
Tamoxifen is a non-steroidal drug from the triphenylethylene group, possessing a combined spectrum of pharmacological action as both an estrogen antagonist and agonist in various tissues. In patients with breast cancer, tamoxifen primarily exhibits an anti-estrogenic effect in tumor cells, preventing estrogen binding to estrogen receptors.
Tamoxifen and some of its metabolites compete with estradiol for binding sites of cytoplasmic estrogen receptors in breast tissue, uterus, vagina, anterior pituitary, and tumors with high estrogen receptor content. Unlike the estrogen receptor complex, the tamoxifen receptor complex does not stimulate DNA synthesis in the nucleus, but suppresses cell division, leading to regression of tumor cells and their death.
In women with estrogen-positive/unspecified breast tumors, adjuvant therapy with tamoxifen significantly reduces disease recurrence and increases life expectancy up to 10 years. A more pronounced effect is achieved with treatment lasting five years, rather than 1-2 years, and is independent of age, menopausal status, tamoxifen dose, or auxiliary chemotherapy.
Approximately 10-20% of postmenopausal women experience a reduction in total cholesterol and low-density lipoprotein concentrations in blood plasma with tamoxifen. Additionally, there are reports that tamoxifen preserves bone mineral density in postmenopausal women.
Variability in clinical response to tamoxifen may be associated with CYP2D6 isoenzyme polymorphism.
Low metabolic rate may be associated with reduced therapeutic response. Recommendations for treating "slow" CYP2D6 isoenzyme metabolizers have not been developed.

Pharmacokinetics
After oral administration, tamoxifen is well absorbed. Maximum serum concentration is reached within 4 to 7 hours after a single dose. Steady-state concentration of tamoxifen in blood serum when using 20-40 mg/day is usually achieved after 3-4 weeks of administration. Protein binding in blood plasma is 98%. It is metabolized in the liver, forming several metabolites.
The main serum metabolite, N-desmethyltamoxifen, and subsequent metabolites possess almost the same anti-estrogenic properties as the original substance. Tamoxifen and its metabolites accumulate in the liver, lungs, brain, pancreas, skin, and bones. Tamoxifen is primarily metabolized by the CYP3A4 isoenzyme to N-desmethyltamoxifen, which is further metabolized by the CYP2D6 isoenzyme to another active metabolite - endoxifen. In patients with CYP2D6 enzyme deficiency, endoxifen concentration is approximately 75% lower than in patients with normal CYP2D6 activity. Use of strong CYP2D6 isoenzyme inhibitors similarly reduces endoxifen blood concentration.
Elimination of tamoxifen from the body is biphasic, with an initial half-life of 7 to 14 hours and a subsequent slow terminal half-life of 7 days. It is excreted mainly as conjugates, primarily through the intestine, with only small amounts eliminated by the kidneys.

Indications for Use:

- adjuvant therapy for early estrogen receptor-positive breast cancer;
- treatment of locally advanced or metastatic breast cancer with estrogen-positive receptors;
- breast cancer (including in men after castration).

The drug may also be used for other solid tumors resistant to standard treatment methods, with estrogen receptor hyperexpression.

Contraindications:

- Hypersensitivity to tamoxifen and/or any other component of the drug
- Pregnancy and breastfeeding
- Pediatric age (under 18 years)

Caution:

Renal insufficiency, diabetes mellitus, eye diseases (including cataracts), deep vein thrombosis and thromboembolism (including in medical history), hyperlipidemia, leukopenia, thrombocytopenia, hypercalcemia, concurrent therapy with indirect anticoagulants, rare hereditary forms of lactose intolerance, lactase deficiency or glucose/galactose absorption disorders (as the tablet contains lactose).

Use During Pregnancy and Breastfeeding:

Tamoxifen Hexal is contraindicated during pregnancy. There are reports of spontaneous abortions, congenital malformations, and fetal death in women taking tamoxifen during pregnancy, although a causal relationship was not established.
Breastfeeding is impossible during tamoxifen therapy, as it inhibits lactation. Upon discontinuation of tamoxifen, milk production does not resume for several months due to the persistent therapeutic effect. It is unknown whether tamoxifen passes into breast milk, so when treatment is necessary, breastfeeding should be discontinued.

Method of Administration and Dosage:

Oral use. Tablets should be taken whole, swallowed with a small amount of liquid, once in the morning or divided into two doses, morning and evening. Dosing regimen is usually established individually depending on indications. Maximum daily dose is 40 mg. The standard recommended dose is 20 mg of tamoxifen. If signs of disease progression appear, medication is discontinued. Treatment duration depends on disease severity, typically requiring long-term treatment. As adjuvant therapy for breast cancer in women, recommended treatment duration is about 5 years.

Side Effects:

According to the World Health Organization (WHO), adverse reactions are classified by frequency as follows:
Immune System Disorders:
Hypersensitivity
Blood and Lymphatic System Disorders:
Common: Anemia
Uncommon: Leukopenia, thrombocytopenia
Rare: Agranulocytosis, neutropenia
Very rare: Pancytopenia
Endocrine System Disorders:
Common: Hypercalcemia (especially in patients with bone metastases at treatment onset)
Metabolism and Nutrition Disorders:
Very common: Fluid retention
Common: Increased triglyceride concentration in plasma

Very rare: Significant plasma triglyceride elevation sometimes with pancreatitis
Unknown frequency: Weight gain, anorexia
Nervous System Disorders:
Common: Headache, dizziness
Unknown frequency: Depression, confusion, photophobia, drowsiness
Ophthalmologic Disorders:
Common: Visual disturbances (sometimes reversible, including cataracts, retinopathy, corneal changes)
Rare: Optic nerve neuropathy, optic neuritis (rarely leading to blindness)
Vascular Disorders:
Common: Leg cramps, transient ischemic attacks, thromboembolism including pulmonary embolism, deep vein thrombosis
Uncommon: Stroke
Respiratory Disorders:
Uncommon: Interstitial pneumonitis
Gastrointestinal Disorders:
Very common: Nausea
Common: Vomiting, diarrhea, constipation
Hepatobiliary Disorders:
Common: Increased liver enzyme activity, fatty liver dystrophy
Uncommon: Liver cirrhosis
Very rare: Cholestasis, hepatitis, jaundice, liver cell necrosis, liver failure (including fatal)
Skin and Subcutaneous Tissue Disorders:
Very common: Rash
Common: Urticaria, alopecia, hypersensitivity reactions
Rare: Vasculitis
Very rare: Systemic lupus erythematosus, polymorphic erythema, Stevens-Johnson syndrome, bullous pemphigoid
Musculoskeletal and Connective Tissue Disorders:
Common: Myalgia
Very rare: Ossalgia (bone pain)
Reproductive System and Breast Disorders:
Very common: Vaginal bleeding, vaginal discharge, menstrual cycle disruption
Common: Genital itching, uterine fibroid enlargement, endometrial proliferative changes
Uncommon: Endometrial cancer
Rare: Ovarian cysts, uterine sarcoma, vaginal polyps, reduced libido in men, impotence in men
At treatment onset, local disease exacerbation may occur - temporary increase in soft tissue formations, sometimes with pronounced erythema - which usually resolves within two weeks.

Overdose:

Acute tamoxifen overdose in humans has not been observed. Overdose is expected to intensify side effects related to the drug's pharmacological action. Rare reports suggest standard dosing multiple times daily may prolong QT interval.
Treatment: No specific antidote exists; treatment should be symptomatic.

Drug Interactions:

When tamoxifen is used simultaneously with cytostatics, thrombosis risk increases.
Reports exist of tamoxifen enhancing anticoagulation effects of coumarin-based drugs like warfarin (requiring careful dose monitoring).
Drugs reducing calcium excretion (e.g., thiazide diuretics) may increase hypercalcemia risk.
Concurrent use with:
Tegafur: May develop chronic active hepatitis and liver cirrhosis
Hormonal drugs (especially estrogen-containing contraceptives): Weakens specific effects of both drugs
CYP3A4 metabolizing drugs: Possible reduced tamoxifen plasma concentration
CYP2D6 inhibitors (paroxetine, fluoxetine): Potentially reduced tamoxifen effectiveness
Bromocriptine: Increases tamoxifen and N-desmethyltamoxifen plasma concentration
Avoid simultaneous use with anastrozole.

Special Instructions:

Women using Tamoxifen Hexal require regular gynecological examination.
Increased endometrial cancer and uterine sarcoma risks exist.
Discontinue if vaginal bleeding occurs.
Periodic monitoring recommended:
Blood coagulation indicators
Calcium levels
Blood count
Liver function
Blood pressure
Ophthalmologic examination
Initial ophthalmologic examination advised. Monitor vision changes

during treatment.
Patients with hyperlipidemia should track cholesterol and triglyceride levels.
Mechanical contraception recommended during and three months after treatment due to potential ovulation induction.

Impact on Vehicle Driving and Machinery Operation:

Caution advised due to potential side effects like dizziness, drowsiness, vision disturbances. Avoid potentially dangerous activities requiring heightened concentration.

Packaging:

Tablets: 10 mg, 20 mg, 30 mg, 40 mg 10 tablets per blister pack 3 or 10 blister packs per cardboard box with instruction manual

Storage Conditions:

Temperature: Not above 25°C Keep out of children's reach

Shelf Life:

5 years Do not use after expiration date

Pharmacy Dispensing:

Prescription required

Manufacturer:

Hexal AG, Industriestrasse 25, 83607 Holzkirchen, Germany
Produced by Salutis Pharma GmbH, Otto-von-Güricke Allee 1, 39179 Barleben, Germany

These instructions translated from official manufacturer instructions in Russian by Extrapharma online pharmacy