Summary Of Product Characteristics

1. NAME OF MEDICINAL PRODUCT

Tamoxifen 10 mg HEXAL, film-coated tablets
Tamoxifen 20 mg HEXAL, film-coated tablets
Tamoxifen 30 mg HEXAL, film-coated tablets
Tamoxifen 40 mg HEXAL, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tamoxifen 10 mg HEXAL
Each film-coated tablet contains 15.2 mg tamoxifen citrate (corresponding to 10 mg tamoxifen).
Excipient with known effect: each film-coated tablet contains 68,6 mg Lactose (as monohydrate)

Tamoxifen 20 mg HEXAL
Each film-coated tablet contains 30.4 mg tamoxifen citrate (corresponding to 20 mg tamoxifen).
Excipient with known effect: each film-coated tablet contains 137,2 mg Lactose (as monohydrate)

Tamoxifen 30 mg HEXAL
Each film-coated tablet contains 45.6 mg tamoxifen citrate (corresponding to 30 mg tamoxifen).
Excipient with known effect: each film-coated tablet contains 205,8 mg Lactose (as monohydrate)

Tamoxifen 40 mg HEXAL
Each film-coated tablet contains 60.8 mg tamoxifen citrate (corresponding to 40 mg tamoxifen).
Excipient with known effect: each film-coated tablet contains 274,4 mg Lactose (as monohydrate)

~~Other excipients with known effect: Lactose monohydrate and lactose~~

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Tamoxifen 10 mg HEXAL
White, round, biconvex.

Tamoxifen 20 mg HEXAL
White, round, biconvex, with score line on one side. The score line is not for dividing the tablet.

Tamoxifen 30 mg HEXAL
White, round, biconvex.

Tamoxifen 40 mg HEXAL

White, round, biconvex, with score line on one side. The score line is not for dividing the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Adjuvant therapy after primary treatment of breast carcinoma
- Metastatic breast carcinoma

4.2 Posology and method of administration

Dosage
The dose is generally between 20 and 40 mg tamoxifen daily. As a rule, a 20 mg dose of tamoxifen is sufficiently effective.

Children and adolescents
Tamoxifen is contraindicated in children (see section 4.3).

Method of administration
Tamoxifen HEXAL film-coated tablets must be swallowed whole at mealtimes with an adequate amount of liquid (e.g., 1 glass of water).

Duration of use
Treatment with tamoxifen is usually long-term and should be supervised by experienced oncologists.

At the present time, a period of at least 5 years is recommended for adjuvant therapy of early hormone receptor positive breast carcinoma. The optimal length of treatment with tamoxifen is still being investigated.

4.3 Contraindications

- Hypersensitivity to the active ingredient or one of the other excipients listed in section 6.1
- Children and adolescents must not be treated with tamoxifen.
- Pregnancy
- Lactation

4.4 Special warnings and precautions for use

For severe thrombocytopenia, leukocytopenia or hypercalcaemia, the benefits in the individual case must be weighed against the risks, and, if prescribed, particularly close medical monitoring is necessary.

Blood counts, including platelets and serum calcium, as well as liver function, should be regularly checked during the administration of tamoxifen. A check on serum triglycerides may be advisable.

Due to the increased risk of endometrial carcinoma or uterine sarcoma (usually malignant mixed Müllerian tumours) caused by tamoxifen, vaginal bleeding in postmenopause and irregular premenopausal bleeding should be investigated promptly. The underlying mechanism for this is not known, but it could be related to tamoxifen having an effect similar to that of oestrogen.

Female patients who have not had a hysterectomy should have an annual gynaecological examination to check for changes to the endometrium. The doctor should decide how frequently women with tumour metastases should be examined.

~~In premenopausal women who are receiving tamoxifen to treat breast carcinoma, tamoxifen may suppress menstruation (see section 4.8).~~

Patients should have an ophthalmic examination when beginning treatment with tamoxifen.

If changes to visual acuity occur during treatment with tamoxifen (cataracts and retinopathy), an ophthalmic examination must be conducted urgently, as many changes seen in the early stage regress after discontinuing the therapy.

Isolated cases of secondary malignancies after treatment with tamoxifen are known from clinical studies, affecting organs other than the endometrium and the contralateral breast. To date, no causal connection with tamoxifen has been established, so that the clinical significance of these findings is unclear.

The risk of microvascular flap complications in microsurgical breast reconstruction at a later time can be increased by tamoxifen.

It has been shown in the literature that poor CYP2D6 (cytochrome P450) metabolisers have a lower plasma endoxifen level. Endoxifen is one of the most important active metabolites of tamoxifen (see section 5.2).

Concomitant administration of medicinal products that inhibit the enzyme CYP2D6 can result in a reduced concentration of the active metabolite, endoxifen. For this reason, the administration of strong CYP2D6 inhibitors during tamoxifen therapy (e.g., paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should be avoided as much as possible.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported with the use of Tamoxifen HEXAL. At the time of prescription, patients should be advised of the signs and symptoms and closely monitored for skin reactions. If signs and symptoms suggestive of these side effects occur, Tamoxifen HEXAL should be discontinued immediately and, if necessary, alternative therapy should be considered. If the patient has developed a serious side effect such as SJS or TEN while using Tamoxifen HEXAL, treatment with Tamoxifen HEXAL must not be re-initiated in this patient at any time.

Tamoxifen may induce or worsen symptoms of angioedema in patients with hereditary angioedema.

The use of Tamoxifen HEXAL may lead to positive doping test results. Abuse of the medicine Tamoxifen HEXAL for doping purposes can endanger your health.

Children and adolescents
In a non-controlled study, 28 girls aged 2-10 years old with McCune-Albright syndrome received 20 mg tamoxifen daily for a period of up to 12 months. Mean uterine volume increased in the course of the first 6 months and had doubled at the end of the one-year study period. This result concurs with the pharmacodynamic properties of tamoxifen, although no causal relationship has been established (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

Hormone preparations, in particular those containing oestrogen (e.g., oral contraceptives) should not be taken during treatment with tamoxifen, as it is possible that each would reduce the effect of the other.

When tamoxifen and the aromatase inhibitor letrozole were administered concomitantly, plasma letrozole concentrations were reduced by 37%. Concomitant use of tamoxifen and aromatase inhibitors as adjuvant therapy did not improve efficacy compared with treatment with tamoxifen alone.

Platelet aggregation inhibitors should not be administered with tamoxifen, to avoid increasing the risk of bleeding during a possible phase of thrombocytopenia.

Combined administration of tamoxifen and coumarin anticoagulants can cause a modification of the coagulation rates (prolongation of the prothrombin time). Concomitant administration of the two medicinal products therefore requires the coagulation status to be closely monitored (especially at the start of treatment).

There are indications of an increased incidence of thromboembolic events during treatment with tamoxifen, including deep vein thrombosis and pulmonary embolism, (see section 4.8). The frequency is increased with simultaneous chemotherapy.

Tamoxifen and its principal metabolites are potent inhibitors of cytochrome P450 oxidases. The effect of tamoxifen on the metabolism and excretion of other cytotoxic medicinal products which are activated by these enzymes, such as cyclophosphamide, is not known.

The principal metabolic pathway known for tamoxifen is demethylation, catalysed by CYP3A4 enzymes. The literature describes pharmacokinetic interactions with substances that induce the CYP3A4 enzymes (such as rifampicin) causing a reduction in the plasma tamoxifen concentration. The clinical relevance of these interactions has not yet been elucidated.

There are reports in the literature of a pharmacokinetic interaction with inhibitors of the enzyme CYP2D6 (cytochrome P450) that causes the plasma concentration of one of the more active forms of tamoxifen to be reduced by 65-75% (e.g., endoxifen). In studies, tamoxifen has been shown to be less effective following concomitant administration of SSRI antidepressants (e.g., paroxetine). Since reduction in the efficacy of tamoxifen cannot be excluded, concomitant administration of strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should be avoided as much as possible (see sections 4.4 and 5.2).

Children and adolescents

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is insufficient experience in the use of tamoxifen during pregnancy and lactation in humans. Animal studies have shown reproductive toxicity (see section 5.3). There are a few reports of spontaneous abortion, birth defects and foetal death in women who have

taken tamoxifen, although no causal relationship has been clearly established. Tamoxifen is contraindicated during pregnancy (see section 4.3). Therefore, the possibility of pregnancy should be excluded prior to starting treatment.

Women should be advised not to become pregnant during treatment with tamoxifen and be informed of the potential risks for the foetus if pregnancy were to occur during, or up to 2 months after treatment with tamoxifen. A reliable, non-hormonal form of contraception should be ensured during the treatment and for up to two months after ending it (see also section 4.5).

Lactation

Limited data indicate that Tamoxifen HEXAL and its active metabolites are excreted in breast milk and accumulate over the time. Therefore, the use of the drug is not recommended during breastfeeding. When deciding whether to wean or discontinue using Tamoxifen HEXAL, the importance of the drug for the mother should be taken into consideration.

In humans, at a dose of 20 mg twice per day, tamoxifen inhibits lactation. Milk production is not resumed after discontinuing the therapy. Furthermore, it is not known whether tamoxifen is excreted in breast milk. Tamoxifen is therefore contraindicated during lactation. If treatment is required, breast-feeding must be discontinued.

Fertility

In premenopausal women, tamoxifen may suppress menstruation (see section 4.8). For results from pre-clinical studies, see section 5.3.

4.7 Effects on ability to drive and operate machinery

It is unlikely that tamoxifen affects the ability to drive or operate machinery. However, fatigue, drowsiness and visual impairment have been reported during treatment with tamoxifen. Patients in whom these symptoms persist should be cautious when driving or operating machinery.

4.8 Side effects

Summary of the safety profile

The side effects that occur are the result either of the pharmacological mechanism of action of the medicinal substance (such as, hot flushes, vaginal bleeding, vaginal discharge, vulvar pruritus and pain in the area of diseased tissue) or are general adverse reactions such as gastrointestinal intolerance, headaches, drowsiness, fluid retention and alopecia.

Tabulated list of side effects

Unless indicated otherwise, the frequencies below have been determined from the reports of the side effects in a large phase III study conducted over 5 years in 9,366 postmenopausal women with operable breast cancer. Unless indicated otherwise, the degree of frequency within the comparative treatment group has not been taken into account, nor whether the investigator considered there to be a causal relationship with the study medication.

The frequency of side effects is divided into the following categories:

Very common	(≥ 1/10)
Common	(≥ 1/100 to < 1/10)
Uncommon	(≥ 1/1,000 to < 1/100)
Rare	(≥ 1/10,000 to < 1/1,000)
Very rare	(<1/10,000)
Not known	(frequency cannot be estimated from available data)

Blood and lymphatic system disorders
Common: transient anaemia
Uncommon: leucopenia, transient thrombocytopenia (usually with values from 80,000 to 90,000/microlitre, occasionally even lower)
Rare: agranulocytosis[1], neutropenia[1]
Very rare: severe neutropenia, pancytopenia[3]

Nervous system disorders
Common: drowsiness, headaches, sensory disorders (including paraesthesia and dysgeusia)

Eye disorders
Common: only partially reversible vision disorders due to cataracts, corneal opacity (rare) and/or retinopathy (the risk of cataracts increases with the duration of tamoxifen administration)
Rare: optic neuropathy[1], optic neuritis (a small number of patients have become blind)

Respiratory, thoracic and mediastinal disorders
Uncommon: interstitial pneumonitis

Gastrointestinal disorders
Very common: nausea
Common: vomiting, diarrhoea, constipation

Skin and subcutaneous tissue disorders
Very common: skin rash (rarely as erythema multiforme[1], Stevens-Johnson syndrome[1] or bullous pemphigoid[1])
Common: alopecia, sensitivity reactions, including rare cases of angioneurotic oedema
Rare: cutaneous vasculitis[1], toxic epidermal necrolysis
Very rare: cutaneous lupus erythematosus[4]
Not known: exacerbation of hereditary angioedema

Musculoskeletal and connective tissue and bone disorders
Common: myalgia

Endocrine disorders
Uncommon: hypercalcaemia in patients with bone metastases, especially at the beginning of therapy

Metabolism and nutrition disorders
Very common: fluid retention
Common: increase in serum triglycerides
Very rare: severe hypertriglyceridaemia, occasionally associated with pancreatitis

Vascular disorders

Common: ischaemic cerebrovascular events, lower leg cramps, thromboembolic events, including deep vein thrombosis, microvascular thrombosis and pulmonary embolism (the frequency of venous thromboembolism is increased with concomitant chemotherapy)
Uncommon: Stroke[2]

General disorders and administration site conditions
Very common: hot flushes, partly due to the anti-oestrogen action of tamoxifen, fatigue
Rare: bone pain and pain in the area of the diseased tissue at the start of treatment as a sign of the response to tamoxifen[1]

Hepatobiliary disorders
Common: changes to liver enzyme parameters, development of fatty liver
Uncommon: liver cirrhosis
Rare: cholestasis[1], hepatitis, jaundice, liver cell necrosis[1], damage to liver cells[1], liver failure[1]
Some cases of severe liver diseases have been fatal.

Reproductive system and breast disorders
Very common: vaginal discharge, changes in the cycle up to complete suppression of menstruation in the premenopausal period[3], vaginal bleeding
Common: vulvar pruritus, enlargement of uterine myomas, proliferative changes to the endometrium (endometrial neoplasia, endometrial hyperplasia, endometrial polyps and rare cases of endometriosis[1])
Uncommon: endometrial carcinoma
According to present knowledge, the risk of endometrial carcinoma becomes two to four times greater as the length of treatment with tamoxifen increases, compared to women not treated with tamoxifen.
Rare: ovarian cysts[1], uterine sarcoma (usually malignant mixed Müllerian tumours)[1], vaginal polyps[1]

Congenital, familial and genetic disorders
Very rare: porphyria cutanea tarda[4]

Injury, poisoning and procedural complications
Very rare: "radiation recall" phenomenon

[1]This side effect did not occur in the tamoxifen arm (n=3,904) of the ATAC study. However, there have been reports of the adverse reaction in other studies or from other sources. Frequency has been calculated using the upper limit of the 95% confidence interval as the point estimate (based on 3/x, x being the total number, e.g., 3/3,094). This produced the calculation 3/3,094, which corresponds to the frequency category of "rare".
[2] Based on data from the NSABP P-1 study
[3] Not based on data from the ATAC study
[4] This event was not observed in the ATAC study or in other large clinical studies. Frequency has been calculated using the upper limit of the 95% confidence interval as the point estimate (based on 3/x, x being the total number of 33,201 patients in large clinical trials). This produced the calculation 3/33,201, which corresponds to the frequency category of "very rare".

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit-risk ratio of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the

Bundesinstitut für Arzneimittel und Medizinprodukte [Federal Institute for Drugs and Medical Devices]
Abt. Pharmakovigilanz [Pharmacovigilance Dept.]
Kurt-Georg-Kiesinger Allee 3
D-53175 Bonn
Website: /www.bfarm.de

4.9 Overdose

Symptoms of an overdose

Little is known about overdose in humans. At doses of 160 mg/m^2 daily and above, ECG changes were observed (prolongation of the QT interval), and neurotoxicity (tremor, hyperreflexia, unsteady gait and dizziness) occurred at 300 mg/m^2 daily.

Theoretically, anti-oestrogen adverse reactions produced through overdose should be stronger. From data from animal studies using extreme overdose (100–200 times the therapeutic dose), it can be concluded that oestrogen effects are also possible.

Treatment measures in the case of an overdose

There is no specific antidote available. It is therefore necessary to initiate a symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hormone antagonists and related agents - antiestrogens
ATC Code: L02BA01

Tamoxifen competitively inhibits oestrogens from binding to cytoplasmic hormone receptors. Consequently, cell division in oestrogen-dependent tissues is reduced. In 50-60% of cases of metastatic breast carcinoma, complete or partial remission occurs, especially of soft tissue and bone metastasis, if oestrogen receptors have been found to be present in the tumour tissue. If the hormone receptor status is negative, particularly of the metastases, objective remission is only observed in approximately 10% of cases. In women with oestrogen receptor positive tumours or tumours of unknown receptor status, significantly fewer recurrences and an increased 10-year survival rate have been found due to adjuvant tamoxifen treatment, a considerably greater effect being achieved with 5-year treatment than with a period of treatment of 1 or 2 years. It has been shown that this benefit occurs irrespective of age and menopause status, or of the dose of tamoxifen or additional chemotherapy.

Clinical experience has shown that in postmenopausal women tamoxifen reduces total blood cholesterol and LDL by 10-20%. Moreover, the bone density of postmenopausal women is reported to be preserved.

CYP2D6 polymorphism may be associated with a distinct response to tamoxifen. The “poor metaboliser status” may be accompanied by a reduced response. The consequence of this for the treatment of poor CYP2D6 metabolisers is not yet completely known (see sections 4.4, 4.5 and 5.2).

CYP2D6 genotype

Clinical data indicate that in patients homozygous for the non-functional CYP2D6 allele, tamoxifen treatment of breast cancer may be less effective. Available studies were conducted mainly in postmenopausal women (see sections 4.4 and 5.2).

Children and adolescents
In a non-controlled study in a heterogeneous group of 28 girls aged 2-10 years with McCune-Albright syndrome, 20 mg tamoxifen was given daily for up to 12 months. Of the patients who reported vaginal bleeding before the study, 62% (13 out of 21) had no vaginal bleeding in the first 6 months and 33% (7 out of 21) had none throughout the entire study. Mean uterine volume increased in the course of the first 6 months and had doubled at the end of the one-year study period. This result concurs with the pharmacodynamic properties of tamoxifen, although no causal relationship has been established. There are no long-term data on the safety of use in children. In particular, the effect on growth, puberty and general development has not been investigated.

5.2 Pharmacokinetic properties

Tamoxifen is well absorbed. Maximum serum concentrations are reached 4–7 hours after oral ingestion. Plasma albumin binding is high at 98%. The terminal plasma half-life is 7 days on average. Tamoxifen is metabolised to a considerable extent. Tamoxifen is mainly metabolised by the enzyme CYP3A4 to N-desmethyltamoxifen, which is in turn metabolised by the enzyme CYP2D6 to the active metabolite 4-hydroxy-N-desmethyltamoxifen (endoxifen). Patients lacking CYP2D6 exhibit an approximately 75% lower endoxifen concentration than patients with normal CYP2D6 activity.

The administration of strong CYP2D6 inhibitors reduces the concentration of circulating endoxifen to the same extent.

The principal metabolite in the serum, N-desmethyltamoxifen and other metabolites have virtually the same anti-oestrogen properties as the parent substance. Tamoxifen and its metabolites accumulate in the liver, lungs, brain, pancreas, skin and bones. With chronic therapy, tamoxifen accumulates in the serum due to marked enterohepatic circulation. With a dose of 20-40 mg/day, a steady state is not reached for at least 4 weeks.

Elimination is predominantly with the faeces in the form of different metabolites.

Children and adolescents
In a non-controlled study, 28 girls aged 2-10 years old with McCune-Albright syndrome received 20 mg tamoxifen daily for a period of up to 12 months. An age-dependent decrease in clearance was observed and an increase in exposure (AUC) with values that in the youngest patients were up to 50% higher than in adults.

5.3 Preclinical safety data

Chronic toxicity trials have been conducted in rats and mice for up to a period of 15 months. These animal species showed histopathological changes to the reproductive organs that could be explained by the pharmacological properties of tamoxifen and were generally reversible. In addition, cataracts were observed.

Studies in various *invivo* and *invitro* systems confirm that tamoxifen is potentially genotoxic following hepatic activation.

Liver tumours in rats and gonadal tumours in mice have been observed in long-term studies. The clinical significance of these findings is unclear.

Data from animal studies and clinical reports indicate an increased risk of formation of endometrial tumours.

Based on the anti-oestrogen action of the substance, tamoxifen inhibits ovulation and the reproductive cycle of female rats, as expected. Once the administration of tamoxifen ceased, fertility was recovered within weeks. There was no effect on the development or reproductive function in young rats whose mothers had previously been treated with tamoxifen.

At low concentrations, tamoxifen prevents implantation and leads to abortion at doses above 2 mg/kg/day. Embryo toxicity studies in several animal species have produced no evidence of teratogenic effects; embryo mortality occurred in rabbits at doses from 0.5 mg/kg/day.

Intrauterine exposure of mice to tamoxifen during foetal development and the treatment of neonate rats and mice with the substance resulted in damage to the female reproductive organs, detectable in adulthood.

Adult female animals also showed regressive changes to their reproductive organs after long-term therapy with doses over 0.05 mg/kg/day. A reduction in testicle weight and spermiogenesis has been described in male rats after short and long-term treatment due to the inhibition of gonadotropin secretion in the pituitary gland.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

- Sodium carboxymethyl starch (type A) (Ph.Eur.)
- Microcrystalline cellulose
- Lactose monohydrate
- Magnesium stearate (Ph.Eur.) [vegetable-derived]
- Povidone K25

Film coating

- Lactose
- Hypromellose
- Macrogol 4,000
- Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/aluminium blister packs

Packs of 30 and 100 film-coated tablets
Tamoxifen 20 mg HEXAL
Packs of 30, 98 and 100 film-coated tablets

Tamoxifen 30 mg HEXAL
Packs of 30 and 100 film-coated tablets

Tamoxifen 40 mg HEXAL
Packs of 30 and 100 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Unused medicinal product or waste material should be disposed of according to national regulations.

7. MARKETING AUTHORISATION HOLDER
Hexal AG
Industriestraße 25
83607 Holzkirchen
Telephone: 08024/908-0
Fax: 08024/908-1290
Email: medwiss@hexal.com

8. MARKETING AUTHORISATION NUMBERS
Tamoxifen 10 mg HEXAL
6255.00.00

Tamoxifen 20 mg HEXAL
6255.01.00

Tamoxifen 30 mg HEXAL
14440.01.00

Tamoxifen 40 mg HEXAL
6255.02.00

9. DATE OF FIRST AUTHORISATIONS/RENEWAL OF THE AUTHORISATIONS
Tamoxifen 10 mg/20 mg/40 mg HEXAL
Date of first authorisation: 22 May 1985
Date of last renewal of authorisations: 14 November 2006

Tamoxifen 30 mg HEXAL
Date of first authorisation: 21 November 1989
Date of last renewal: 10 January 2006

10. DATE OF REVISION OF THE TEXT
May 2021

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription