SUMMARY OF PRODUCT CHARACTERISTICS TAMOXIFEN

1. NAME OF THE MEDICINAL PRODUCTS

Tamoxifen 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tamoxifen 20 mg

1 film-coated tablet contains 30.4 mg tamoxifen citrate (equivalent to 20 mg tamoxifen).

Excipient with known effect: Lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Tamoxifen 20 mg

White, round, convex, with score line on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adjuvant therapy after primary treatment of breast carcinoma

Metastasised breast carcinoma

4.2 Posology and method of administration

Posology

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

Paediatric population

Tamoxifen is contraindicated in children (see section 4.3).

Method of administration

Tamoxifen 20 mg film-coated tablets must be swallowed whole at mealtimes with an adequate amount of liquid (e.g. 1 glass of water).

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

- Known hypersensitivity to the active substance or to any of the 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

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

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

On account of the increased risk of endometrial carcinoma or uterine sarcoma (usually malignant mixed Müllerian tumours), due to tamoxifen, the causes of vaginal bleeding in the postmenopausal period or irregular bleeding in premenopausal women must be clarified without delay. 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, it 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 far as possible.

The use of Tamoxifen HEXAL may lead to positive doping test results. It is not possible to predict the health consequences of using tamoxifen as a doping substance; serious health risks cannot be ruled out.

Female patients with a rare hereditary galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take Tamoxifen HEXAL.

Paediatric population

In a non-controlled study, 28 girls aged 2-10 years old with McCune-Albright syndrome received 20 mg tamoxifen per day 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 modification of coagulation rates (prolongation of the prothrombin time). Concomitant administration of the two products therefore requires the coagulation status to be closely monitored (above all at the start of treatment).

There are indications of 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 concomitant 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 far as possible (see sections 4.4 and 5.2).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is insufficient data on the use of tamoxifen during human pregnancy and while breastfeeding. Experimental 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). The possibility of pregnancy should therefore be excluded before the start of 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

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

Fertility

Tamoxifen can suppress menstruation in premenopausal women (see section 4.8). For results from pre-clinical studies, see section 5.3.

4.7 Effects on ability to drive and use machines

It is unlikely that Tamoxifen affects the ability to drive and use machines. However, fatigue, drowsiness, and visual impairment have been reported during treatment with Tamoxifen. Patients for whom these symptoms persist should be careful when driving a vehicle or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The undesirable 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 undesirable effects such as gastrointestinal intolerance, headaches, drowsiness, fluid retention and alopecia.

List of undesirable effects

Unless indicated otherwise, the frequencies below have been determined from the reports of the undesirable 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 frequencies of undesirable effects are based on 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 the available data)

Blood and lymphatic system disorders

Common: transient anaemia

Uncommon: leukopenia, transient thrombocytopenia (usually with values from 80,000 to 90,000/microlitre, occasionally even lower)

Rare: agranulocytosis,[1] neutropenia[1]

Very rare: severe modifications to the blood count (neutropenia, pancytopenia[3])

Nervous system disorders

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

Eye disorders

Common: vision disorders, only partially reversible, 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 tract 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]

Very rare: cutaneous lupus erythematosus[4]

Musculoskeletal, connective tissue and bone disorders

Common: Myalgia

Endocrine disorders

Uncommon: hypercalcaemia in patients with bone metastases, above all 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 complaints at the site of administration

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 values, development of fatty liver

Uncommon: liver cirrhosis

Rare: cholestasis,[1] hepatitis, jaundice, liver cell necrosis,[1] damage to liver cells,[1] liver failure[1]

Certain 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 an endometrial carcinoma becomes 2 to 4 times greater as the length of treatment with tamoxifen increases, compared with women not treated with tamoxifen.

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]

[1] This undesirable effect did not occur in the tamoxifen arm (n=3,904) of the ATAC study. There have been reports of the undesirable effect however 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 13,357 patients in the large clinical studies). This produced the calculation 3/13,357, 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 balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system shown.

Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)

Abt. Pharmakovigilanz (Pharmacovigilance Dept.)

Kurt-Georg-Kiesinger Allee 3

53175 Bonn, Germany

Website: http://www.bfarm.de

4.9 Overdose

Symptoms of overdose

Little is known concerning overdose in humans. At doses of 160 mg/m^2/day and over, ECG changes were observed (prolongation of the QT interval), and neurotoxicity (tremor, hyperreflexia, unsteady gait and dizziness) occurred at 300 mg/m^2/day. Theoretically, in the event of an overdose the intensification of anti-oestrogen undesirable effects should be expected. From data from animal studies using extreme overdose (100–200 times the therapeutic dose), it can be concluded that oestrogen effects are also possible.

Measures for treating overdose

There is no specific antidote. The treatment initiated must therefore be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents – endocrine therapy – hormone antagonists and related agents - anti-oestrogens - tamoxifen

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 metastasing breast carcinoma, complete or partial remission occurs, above all 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 approx. 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, poor metaboliser status possibly being associated here with a reduced response. The consequence of this for the treatment of poor CYP2D6 metabolisers is not as yet completely understood (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. The studies available were conducted mainly in postmenopausal women (see sections 4.4 and 5.2).

Paediatric population

In a non-controlled study, a heterogeneous group of 28 girls aged 2-10 years old with McCune-Albright syndrome received 20 mg tamoxifen per day for a period of 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. The effect on growth, puberty and general development has not been investigated, in particular.

5.2 Pharmacokinetic properties

Tamoxifen is well absorbed. Maximum serum concentrations are reached 4–7 hours after oral ingestion. Plasma protein binding is high at 98%. The terminal plasma half-life is on average 7 days. Tamoxifen is metabolised to a considerable extent. It 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.

Paediatric population

In a non-controlled study, 28 girls aged 2-10 years old with McCune-Albright syndrome received 20 mg tamoxifen per day for a period of 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 *in vivo* and *in vitro* 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.

On the basis of its anti-oestrogen action, 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 development or reproductive function in young rats whose mothers had previously been treated with tamoxifen.

At low concentrations, tamoxifen prevents implantation, and at doses above 2 mg/kg/day lead to abortion. 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 inhibition of gonadotropin secretion in the pituitary gland.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Sodium starch glycolate, type A (Ph.Eur)
- Microcrystalline cellulose
- Hypromellose
- Lactose monohydrate
- Macrogol 4,000
- Magnesium stearate (Ph.Eur.)
- Povidone K 25
- Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/aluminium blister packs

Tamoxifen 20 mg

Original packages with 30, 98 and 100 film-coated tablets

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SANDOZ GmbH,KUNDL BIOCHEMIESTRASSE 106250 AUSTRIA.

8. MARKETING AUTHORISATION NUMBERS- to be allocated after registration.

9. DATE OF FIRST AUTHORISATIONS/RENEWAL OF THE AUTHORISATIONS- to be allocated after registration

10. DATE OF REVISION OF THE TEXT

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal products subject to medical prescription