SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCTS
Tamoxifen Sandoz 10 mg, film-coated tablets
Tamoxifen Sandoz 20 mg, film-coated tablets
Tamoxifen Sandoz 30 mg, film-coated tablets
Tamoxifen Sandoz 40 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Tamoxifen 10 mg
One film-coated tablet contains 15.2 mg tamoxifen citrate (equivalent to 10 mg tamoxifen)

Tamoxifen 20 mg
One film-coated tablet contains 30.4 mg tamoxifen citrate (equivalent to 20 mg tamoxifen)

Tamoxifen 30 mg
One film-coated tablet contains 45.6 mg tamoxifen citrate (equivalent to 30 mg tamoxifen)

Tamoxifen 40 mg
One film-coated tablet contains 60.8 mg tamoxifen citrate (equivalent to 40 mg tamoxifen)

Excipient: lactose monohydrate

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
Film-coated tablet

Tamoxifen 10 mg
White, round, convex

Tamoxifen 20 mg
White, round, convex, scored on one side

Tamoxifen 30 mg
White, round, convex

Tamoxifen 40 mg
White, round, convex, scored on one side

4. CLINICAL PARTICULARS

4.1. Therapeutic indications
- Adjuvant therapy following primary treatment of breast cancer
- Metastatic breast cancer

4.2. Posology and method of administration
In general, the dosage is between 20 and 40 mg tamoxifen per day. A dose of 20 mg tamoxifen is usually sufficiently effective.

Tamoxifen 10 mg/- 20 mg/- 30 mg/- 40 mg film-coated tablets should be taken without chewing together with sufficient liquid (e.g. a glass of water) with meals.

Treatment with tamoxifen is usually long-term therapy and should be carried out by physicians experienced in oncology.

In adjuvant treatment of early hormone receptor-positive breast cancer, duration of treatment of at least 5 years is currently recommended. The optimal duration of tamoxifen therapy remains to be determined.

Tamoxifen is contraindicated in children (see section 4.3).

4.3. Contraindications
- Known hypersensitivity to tamoxifen citrate or to any of the excipients of the medicinal product

- Children and adolescents must not be treated with tamoxifen.

- Pregnancy

- Lactation

4.4. Special warnings and precautions for use
In cases of severe thrombopenia, leukopenia or hypercalcaemia, individual risk-benefit assessment and thorough medical supervision are necessary.

Blood count, serum calcium and liver function should be monitored at regular intervals during use of tamoxifen. Monitoring of triglycerides in serum may be useful.

Due to the elevated risk of endometrial malignancies (including malignant Mullerian tumours) due to tamoxifen, the causes for vaginal bleeding in the post-menopause and irregular bleeding in the pre-menopause should be clarified without delay.

Non-hysterectomized patients should have a gynaecological examination every year in view of endometrial alterations. In patients with metastatic tumours, the physician should decide on the frequency of examinations.

At the beginning of therapy with tamoxifen, an ophthalmic examination should be performed.

If the vision is altered during treatment with tamoxifen, ophthalmic examination is indispensable, as some alterations diagnosed in the early stage subside after cessation of therapy.

Isolated cases of secondary malignancies affecting other organs than the endometrium and the opposite breast are known from clinical studies following the treatment with tamoxifen. No causal link with tamoxifen has been established so far, and the clinical significance of these observations remains unclear.

In an uncontrolled trial in 28 girls aged 2 to 10 years with McCune-Albright syndrome, they received 20 mg tamoxifen daily for up to 12 months' duration. Mean uterine volume increased after 6 months of treatment and doubled at the end of the one-year study. While this finding is in line with the pharmacodynamic properties of tamoxifen, a causal relationship has not been established (see 5.1).

In literature it has been shown that slow metabolisers (poor metabolisers) of the enzyme CYP2D6 (cytochrome P450) have a lowered plasma level of endoxifen, one of the most important active metabolites of tamoxifen (see section 5.2).

Concomitant administration of medicinal products that inhibit the enzyme CYP2D6 may lead to reduced concentrations of the active metabolite endoxifen. Therefore, the administration of potent inhibitors of the enzyme CYP2D6 (e.g. paroxetine, fluoxetine, quinidine, cincalcet or bupropion) should whenever possible be avoided during tamoxifen treatment.

Use of Tamoxifen HEXAL can lead to positive results in doping tests. Health risks secondary to the use of tamoxifen for doping purposes cannot be anticipated, serious health risks cannot be excluded.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Tamoxifen.

4.5. Interaction with other medicinal products and other forms of interaction
No hormonal preparations, especially not those containing oestrogen (e.g. oral contraceptives), should be taken during treatment with tamoxifen, since reciprocal diminution in effect is possible.

In case of concomitant use of tamoxifen and the aromatase inhibitor letrozole, the plasma concentrations of letrozole were reduced by 37%. Concomitant use of tamoxifen and aromatase inhibitors during adjuvant therapy did not show improved efficacy, compared with therapy with tamoxifen alone.

No thrombocyte-aggregation inhibitors should be administered together with tamoxifen so that the bleeding risk during a possible thrombocytopenic phase will not be increased.

Concomitant administration of tamoxifen and anticoagulants of the coumarin type may lead to altered coagulation conditions (prolonged prothrombin time). Therefore, concomitant administration of both medicinal products requires careful monitoring of the coagulation status (especially on initiation of therapy).

Concomitant administration of tamoxifen and aminoglutethimide may lead to a reduction in the plasma tamoxifen level and thus to a reduced effect of tamoxifen.

There is evidence of an increased incidence of thromboembolic incidents, including deep vein thrombosis and pulmonary embolism during treatment with tamoxifen. The frequency is increased during concomitant chemotherapy.

Tamoxifen and its main metabolites are potent inhibitors of oxidases of the cytochrome P450 system. The effect of tamoxifen on the metabolism and excretion of other cytotoxic medicinal products activated via these enzymes (for example cyclophosphamide) is not known.

The known principal pathway for tamoxifen metabolism is demethylation, catalyzed by CYP3A4 enzymes. Pharmacokinetic interactions with substances that induce CYP3A4 enzymes (such as rifampicin), showing a reduction in tamoxifen plasma levels have been reported in literature. The clinical relevance of these interactions is not yet known.

Pharmacokinetic interaction with inhibitors of the enzyme CYP2D6 (cytochrome P450), showing a 65-75% reduction in plasma levels of one of the more active forms of tamoxifen (e.g. endoxifen), has been reported in literature. Reduced efficacy of tamoxifen has been reported in studies after concomitant administration of antidepressants of the SSRI group (e.g. paroxetine). As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 inhibitors (e.g. paroxetine, fluoxetine, quinidine, cinacalcet or bupropion) should whenever possible be avoided (see sections 4.4 and 5.2).

4.6. Pregnancy and lactation
No sufficient experience is available regarding use of tamoxifen in human pregnancy. Animal studies have shown toxicity to reproduction (see 5.3). Tamoxifen is contraindicated during pregnancy (see 4.3). The possibility of pregnancy should therefore be excluded before starting treatment. Reliable, non-hormonal contraception should be ensured during and up to two months after the end of treatment (see also 4.5).

Tamoxifen produces inhibited lactation in humans at a dose of 20 mg twice daily. Lactic production does not start again even if therapy is discontinued. In addition, it is not known whether tamoxifen passes into breast milk. Tamoxifen is therefore contraindicated during lactation. If treatment is necessary, breast-feeding must be stopped.

4.7. Effects on ability to drive and use machines
No studies of the effects on the ability to drive and use machines have been performed.

It must be heeded when driving and using machines that tamoxifen impairs vision and may cause drowsiness.

4.8. Undesirable effects
The evaluation of undesirable effects is based on the following information on frequencies:

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:	(cannot be estimated from the available data)

Blood and lymphatic system disorders

Common:	transient anaemia
Uncommon:	neutropenia, leukopenia, transient thrombocytopenia (mostly with values of 80,000-90,000/µl, uncommonly even lower)
Very rare:	severe neutropenia, pancytopenia
Not known:	agranulocytosis

Nervous system disorders

Common:	drowsiness, headache
Not known:	depressive mood

Eye disorders

Common:	only partially reversible dysopia due to cataracts, corneal opacity and/or retinopathy. The risk of cataracts increases with the duration of tamoxifen intake.
Rare:	optic neuropathy and optic neuritis. Blindness occurred in a small number of cases.

Respiratory, thoracic and mediastinal disorders

Very rare:	interstitial pneumonitis

Gastrointestinal disorders

Common:	nausea
Uncommon:	vomiting

Skin and subcutaneous disorders

Common:	skin rash (very rarely as erythema multiforme, Stevens-Johnson syndrome or bullous pemphigus), alopecia

Uncommon:	hypersensitivity reactions, including angioneurotic oedema
Not known:	cutaneous vasculitis

Endocrine disorders

Uncommon:	hypercalcaemia in patients with bone metastases, particularly at the beginning of therapy

Metabolism and nutrition disorders

Common:	fluid retention, increase in serum triglycerides
Very rare:	severe hypertriglyceridaemia, partially accompanied by pancreatitis

Vascular disorders

Common:	ischaemic cerebrovascular events, leg cramps, thromboembolism, including deep vein thrombosis and pulmonary embolism, particularly in combination with chemotherapeutics
Uncommon:	stroke

General disorders and administration site conditions

Very common:	hot flushes which are partially attributable to the anti-oestrogenic effect of tamoxifen
Common:	at the beginning of therapy, bone pain and pain in the area of affected tissue as a sign of the response to tamoxifen.

Hepatobiliary disorders

Uncommon:	changes in liver enzyme values
Rare:	development of a fatty liver, cholestasis, hepatitis, jaundice
Not known:	agranulocytosis with liver cell necrosis

Reproductive system and breast disorders

Very common:	vaginal discharge, cycle changes up to complete suppression of menstruation in the pre-menopause
Common:	vulvovaginal pruritus, vaginal bleeding, increased size of uterine leiomyomas, proliferative endometrial alterations (endometrial neoplasia, endometrial hyperplasia, endometriosis, endometrial polyps)
Uncommon:	endometrial carcinoma According to current knowledge, the risk of endometrial carcinoma increases to the 2-4fold with increasing duration of treatment with tamoxifen, compared with women not treated with tamoxifen.
Rare:	ovarian cysts, uterine sarcoma.

4.9. Overdose

a) Symptoms of an overdose

Little is known about overdose in humans. At dosages of 160 mg/m^2 daily and more, ECG alterations (prolonged QT time) and at dosages of 300 mg/m^2 daily, neurotoxicity (tremor, hyperreflexia, unsteady gait and vertigo) occurred.

On theoretical grounds, overdose would be expected to cause enhancement of the anti-oestrogenic side effects. Animal studies with extreme overdose (the 100-200 fold of a therapeutic dose) allow the conclusion that oestrogenic effects are also possible.

b) Therapeutic measures in case of an overdose

No specific antidote is available. For this reason, symptomatic treatment should be initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: anti-neoplastic and immunomodulatory agents – endocrine therapy – hormone antagonists and related agents – anti-oestrogens – tamoxifen

ATC Code: L02BA01

Tamoxifen competitively inhibits the binding of oestrogens to cytoplasmic hormone receptors with consecutive decrease in the cell division in oestrogen-dependent tissues. In metastatic breast cancer, complete or partial remission occurs in approx. 50-60% of cases, particularly in soft tissue and bone metastases if oestrogen receptors are found in tumour tissue. In cases of negative hormone receptor status, particularly of the metastases, approx. 10% showed objective remissions. Women with oestrogen receptor-positive tumours or tumours with unknown receptor status who received adjuvant treatment with tamoxifen, experienced significantly less tumour recurrences and had a higher 10-year survival rate. The effect was greater after 5 years of adjuvant treatment compared with 1-2 years of treatment. The benefit appears to be independent of age, menopausal status, daily tamoxifen dose and additional chemotherapy.

In postmenopausal women, clinical experience showed that tamoxifen leads to a reduction in blood total cholesterol and LDL of the order of 10-20%. In addition, maintenance of bone density has been reported in postmenopausal women.

In an uncontrolled study, a heterogeneous group of 28 girls aged 2 to 10 years with McCune-Albright syndrome received 20 mg tamoxifen daily for up to 12 months' duration. Among the patients who reported vaginal bleeding during the pre-study period, 62% (13 out of 21) reported no bleeding for a 6-month period and 33% (7 out of 21) reported no vaginal bleeding for the duration of the study. Mean uterine volume increased after 6 months of treatment and doubled at the end of the one-year study. While this finding is in line with the pharmacodynamic properties of tamoxifen, a causal relationship has not been established. There are no long-term safety data regarding safe use in children. In particular, the long-term effects of tamoxifen on growth, puberty and general development have not been studied.

CYP2D6 polymorphism status may be associated with variability in clinical response to tamoxifen. The poor metaboliser status may be associated with reduced response. The consequences of the findings for the treatment of slow metabolisers of CYP2D6 have not been fully elucidated (see sections 4.4, 4.5 and 5.2).

CYP2D6 genotype
Available clinical data suggest that patients who are homozygote for non-functional CYP2D6 alleles may experience reduced effect of tamoxifen in the treatment of breast cancer. The available studies have mainly been performed in post-menopausal women (see sections 4.4 and 5.2).

5.2. Pharmacokinetic properties
Tamoxifen is well absorbed. Maximum serum levels are achieved 4-7 hours after oral intake. Plasma protein binding is high accounting for 98%. Mean terminal plasma half-life is 7 days. Tamoxifen is extensively metabolised. The main metabolite in serum, N-desmethyltamoxifen, and further metabolites have almost the same anti-oestrogenic properties like the parent compound. Tamoxifen and its metabolites accumulate in liver, lung, brain, pancreas, skin and bones. Due to pronounced enterohepatic circulation, tamoxifen cumulates in chronic therapy in serum. At a dosage of 20-40 mg/day, steady state is reached after 4 weeks at the earliest.

Excretion occurs primarily via the faeces in the form of various metabolites.

In an uncontrolled study where girls between 2 and 10 years of age with McCune-Albright syndrome received 20 mg tamoxifen daily for up to 12 months duration, there was an age-dependent decrease in clearance and an increase in exposure (AUC), with values up to 50% higher in the youngest patients compared with adults.

Tamoxifen is metabolised mainly by the enzyme CYP3A4 to N-desmethyl-tamoxifen which is further metabolised by the enzyme CYP2D6 to the active metabolite 4-hydroxy-N-desmethyl-tamoxifen (endoxifen). In patients devoid of CYP2D6, an about 75% lower concentration of endoxifen was seen, compared with patients with normal CYP2D6 activity.
The administration of potent CYP2D6 inhibitors reduces the circulating endoxifen levels to the same extent.

5.3. Preclinical safety data
Studies of chronic toxicity were performed in rats and mice up to a duration of 15 months. The animal species showed histopathological alterations in reproductive organs which could be explained by the pharmacological properties of tamoxifen and which were usually reversible. In addition, the occurrence of cataracts was observed.

Studies in various *in vivo* and *in vitro* systems have shown that tamoxifen has a genotoxic potential following hepatic activation. Hepatic tumours in rats and gonadal tumours in mice have been observed in long-term studies. The clinical relevance of these findings has not been established.

Data from animal experiments and clinical reports give evidence of an aggravated risk of endometrial tumours.

Tamoxifen prevents implantation at low concentrations and leads to abortions at dosages above 2 mg/kg/day. Embryotoxicity studies in several animal species did not provide any evidence of teratogenic effects, embryolethal effects occurred in rabbits at a dose from 0.5 mg/kg/day.

Intrauterine exposure of mice during foetal development as well as treatment of neonate rats and mice with tamoxifen results in damage to female reproductive organs, which is identifiable in adult age. Adult female animals also showed regressive alterations in reproductive organs after long-term treatment at dosages above 0.05 mg/kg/day. In male rats, reduction in testicular weight and in spermiogenesis induced by inhibition of gonadotropin secretion in hypophysis have been described after short- and long-term treatment.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Carboxymethyl starch sodium (type A) (Ph.Eur.)
Microcrystalline cellulose
Hypromellose
Lactose monohydrate
Macrogol 4,000
Magnesium stearate (Ph.Eur.)
Povidone K 25
Colouring agent titanium dioxide (E 171)

6.2. Incompatibilities
Not applicable

6.3. Shelf life
24 months

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

Tamoxifen 10 mg
Packs containing 30 and 100 film-coated tablets

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

Tamoxifen 30 mg
Packs containing 30 and 100 film-coated tablets

Tamoxifen 40 mg
Packs containing 30 and 100 film-coated tablets

6.6. Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Salutas Pharma GmbH, Barleben, Germany.

8. MARKETING AUTHORISATION NUMBER

04700/06805/REN/2018

9. DATE OF AUTHORIZATION

Oct 25, 2019

10. DATE OF REVISION OF THE TEXT
July 2011

11. GENERAL CLASSIFICATION FOR SUPPLY
Medicinal product subject to medical prescription