SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TAMOXIFEN 10 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Tamoxifen citrate (equivalent to 10 mg tamoxifen)…….15.2 mg
Excipient(s) with known effect:
Lactose (derived from bovine milk)……. 114.4 mg
For the list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
White, round tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TAMOXIFEN is indicated for the treatment of breast cancer.

4.2 Posology and method of administration

Posology/frequency and duration of administration
Adults and elderly: 20-40 mg is administered per day, in divided doses twice daily or as a single dose once daily.

In early-stage breast cancer, it is recommended that hormone therapy be continued for at least 5 years. The physician will decide on the optimum duration of TAMOXIFEN treatment.

Method of administration
For oral use.

Additional information on special populations:
Renal/Hepatic impairment:
There are no sufficient data.

Pediatric population:
Its use in children is not recommended since efficacy and safety have not been established (see sections 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties).

Elderly:
Dose adjustment is not recommended in the elderly.

4.3 Contraindications

Pregnancy: TAMOXIFEN must not be used during pregnancy. A very small number of miscarriages, fetal deaths and birth defects have been reported in women using tamoxifen, but a causal relationship between these cases and drug use has not been established (see section 4.6 for Pregnancy & Lactation).

This medicine must not be used in patients with known hypersensitivity to TAMOXIFEN or any of its ingredients.

Concomitant use with anastrozole is contraindicated.

4.4 Special warnings and precautions for use

Menstruation is suppressed in a proportion of pre-menopausal women receiving TAMOXIFEN for the treatment of breast cancer.

An increased incidence of endometrial changes including hyperplasia, polyps, endometrial cancer, and uterine sarcoma (mostly malignant *mixed Müllerian tumors)* has been reported in association with tamoxifen treatment. The underlying mechanism is unknown, but may be related to the estrogen-like effect properties of TAMOXIFEN. Any patient receiving or having previously received TAMOXIFEN who report abnormal gynecological symptoms, especially vaginal bleeding, or who presents with menstrual irregularities, vaginal discharge and symptoms such as pelvic pain or pressure should be promptly investigated.

It is recommended that patients be examined by a gynecologist prior to use and periodically during treatment and report any abnormal vaginal bleeding to their doctor.

A number of second primary tumors, occurring at sites other than the endometrium and the opposite breast, have been reported in clinical trials, following the treatment of breast cancer patients with tamoxifen. No causal link has been established and the clinical significance of these observations remains unclear.

At several times the normal dose, TAMOXIFEN may cause the development of long QT syndrome / torsades de pointes. It should not be used in patients with diagnosed or suspected congenital long QT syndrome or torsades de pointes.

Venous thromboembolism (VTE)

- A 2-3-fold increase in the risk for VTE has been demonstrated in healthy tamoxifen-treated women (see Section 4.8 Undesirable effects).
- In patients with *breast cancer*, prescribers should obtain careful histories with respect to the patient's personal and family history of VTE. If there is evidence of prothrombotic risk, patients should be screened for thrombophilic factors. Patients who test positive should be counselled regarding their thrombotic risk. The decision to use tamoxifen in these patients should be based on the overall risk to the patient. In selected patients, the use of tamoxifen with prophylactic anticoagulation may be justified (cross-reference section 4.5).
- The risk of VTE is further increased by severe obesity, increasing age and all other risk factors. The risks and benefits should be carefully considered for all patients before treatment with tamoxifen. In patients with *breast cancer*, this risk is also increased by concomitant chemotherapy (see Section 4.5 Interaction with other medicinal products and other forms of interaction). Long-term anti-coagulant prophylaxis may be justified for some patients who have multiple risk factors for VTE.
- Surgery and immobility: In patients treated for *infertility*, tamoxifen should be stopped at least 6 weeks before surgery or long-term immobility (when possible) and re-started only when the patient is fully mobile. For patients with *breast cancer*, tamoxifen treatment should only be stopped if the risk of tamoxifen-induced thrombosis clearly outweighs the risks associated with interrupting treatment. *All* patients should receive appropriate thrombosis prophylactic measures and should include graduated compression stockings for the period of hospitalization, early ambulation, if possible, and anti-coagulant treatment.

- If any patient develops VTE, tamoxifen should be stopped immediately and appropriate anti-thrombosis measures initiated. In patients using tamoxifen for *breast cancer*, the decision to re-start tamoxifen should be made with respect to the overall risk for the patient. In selected patients with *breast cancer*, the continued use of tamoxifen with prophylactic anticoagulation may be justified.
- All patients should be advised to contact their doctors immediately if they become aware of any symptoms of VTE.

TAMOXIFEN may be associated with an increased risk of microvascular flap complications in late breast reconstruction surgery.

In an uncontrolled 12-month clinical trial of 28 girls aged 2 to 10 years with McCune-Albright syndrome (MAS) who took 20 mg of tamoxifen daily, uterine volume increased after 6 months of treatment and doubled at the end of the study one year later. As these findings are consistent with the pharmacodynamic properties of tamoxifen, a causal relationship cannot be established.

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not use this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

When TAMOXIFEN is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur. Where such co-administration is initiated, careful monitoring of the patient is recommended.

When TAMOXIFEN is used in combination with cytotoxic agents, there is increased risk of thromboembolic events occurring (see Section 4.8 Undesirable effects). Because of this increased risk of VTE, thromboprophylaxis should be considered during chemotherapy when these combinations are used.

Use of tamoxifen in combination with anastrozole as adjuvant therapy did not show increased efficacy compared to the use of tamoxifen alone. Concomitant use with anastrozole should be avoided.

Concomitant use of tamoxifen with aromatase inhibitors in adjuvant therapy did not show increased effects compared with tamoxifen alone.

The known pathway for tamoxifen metabolism in humans is demethylation catalyzed by CYP3A4 enzymes. It has been reported in the literature that pharmacokinetic interaction with CYP3A4 in the presence of rifampicin, an enzyme-inducing agent, causes a decrease in tamoxifen plasma levels. The clinical relevance of this is unknown.

Pharmacokinetic interaction with CYP2D6 inhibitors, showing a 65-75% reduction in plasma levels of one of the more active forms of the drug, i.e. endoxifen, has been reported in the literature. Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI antidepressants (e.g. paroxetine) in some studies. 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 Section 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties).

4.6 Pregnancy and lactation

Pregnancy category: D

TAMOXIFEN is contraindicated in pregnant women.

Women with childbearing potential/Birth control (Contraception)
Women should be advised not to become pregnant whilst taking TAMOXIFEN and should use barrier or other non-hormonal contraceptive methods if sexually active. Premenopausal women must be carefully examined before treatment to exclude pregnancy. Women should be informed of the potential risks to the fetus, should they become pregnant whilst taking TAMOXIFEN or within two months of cessation of therapy.

Pregnancy
TAMOXIFEN must not be used during pregnancy. A very small number of miscarriages, fetal deaths and birth defects have been reported in women using tamoxifen, but a causal relationship between these cases and drug use has not been established.

Lactation
It is not known if TAMOXIFEN are excreted in human milk and therefore the drug is not recommended during lactation. The decision to either discontinue nursing or discontinue TAMOXIFEN should take into account the importance of the drug to the mother.

Reproductive ability/Fertility
Tamoxifen was not mutagenic in a range of *in-vitro* and *in-vivo* mutagenicity tests. Tamoxifen was genotoxic in some *in-vitro* and *in-vivo* genotoxicity tests in rodents. Gonadal tumors in mice and liver tumors in rats receiving tamoxifen have been reported in long-term studies. The clinical relevance of these findings has not been established.

Reproductive toxicology studies in rats, rabbits and monkeys have shown no teratogenic potential.

Tamoxifen was associated with changes similar to those caused by estradiol, ethinylestradiol, clomiphene and diethylstilbestrol (DES). Although the clinical relevance of these changes is unknown, some of them, especially vaginal adenosis, are similar to those seen in young women who were exposed to DES in-utero and who have a 1 in 1000 risk of developing clear-cell carcinoma of the vagina or cervix. Only a small number of pregnant women have been exposed to tamoxifen. Such oral exposure has not been reported to cause subsequent vaginal adenosis or clear-cell carcinoma of the vagina or cervix in young women exposed in utero to tamoxifen.

4.7 Effects on ability to drive and use machines
There is no evidence that TAMOXIFEN impairs the ability to drive or use machinery.

4.8 Undesirable effects
Side effects can be classified as either due to the pharmacological action of the drug, e.g. hot flushes, vaginal bleeding, vaginal discharge, pruritus vulvae and tumor flare, or as more general side effects, e.g. gastro-intestinal intolerance, headache, light-headedness and occasionally, fluid retention and alopecia.

When side effects are severe, it may be possible to control them by a simple reduction of dosage (within the recommended dosage range) without loss of control of the disease.

Undesirable side effects of tamoxifen are summarized below.

Frequencies are defined as:
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)

Neoplasms benign and malignant
Common: Uterine myoma
Uncommon: Endometrial cancer
Rare: Uterine sarcoma (mostly malignant mixed Müllerian tumors), tumor flare

Blood and lymphatic system disorders
Common: Anemia, thromboembolic events (including deep vein thrombosis, microvascular thrombosis and pulmonary embolism)
Uncommon: Thrombocytopenia, leukopenia
Rare: Neutropenia, agranulocytosis

Immune system disorders
Common: Hypersensitivity reactions

Metabolism and nutrition disorders
Very common: Fluid retention
Uncommon: Hyperkalemia (in patients with bony metastases)

Nervous system disorders
Common: Ischemic cerebrovascular events, headache, light-headedness, sensory disturbances (paresthesia and dysgeusia)
Rare: Optic neuritis

Eye disorders
Common: Cataracts, retinopathy
Uncommon: Visual disturbances
Rare: Corneal changes, optic neuropathy

Vascular disorders
Very common: Hot flushes

Respiratory, thoracic and mediastinal disorders
Uncommon: Interstitial pneumonia

Gastrointestinal disorders
Very common: Nausea
Common: Vomiting, diarrhea, constipation
Uncommon: Pancreatitis

Hepatobiliary disorders
Common: Changes in liver enzymes, fatty liver
Uncommon: Cirrhosis
Rare: Hepatitis, bile duct obstruction, hepatic failure, hepatocellular injury, hepatic necrosis

Skin and subcutaneous tissue disorders
Very common: Skin rash
Common: Alopecia
Rare: Angioedema, Steven-Johnson syndrome, cutaneous vasculitis, bullous pemphigoid, erythema multiforme
Very rare: Cutaneous lupus erythematosus

Musculoskeletal, connective tissue and bone disorders
Common: Leg cramps, myalgia

Reproductive system disorders
Very common: Vaginal bleeding, vaginal discharge
Common: Vaginal itching, endometrial changes (including endometrial hyperplasia and polyps)
Rare: Endometriosis, cystic ovarian swelling, vaginal polyps

Congenital, familial and genetic disorders
Very rare: *Porphyria cutanea tarda*

Investigations
Common: Elevated triglycerides

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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.

4.9 Overdose and treatment

On theoretical grounds, an overdosage would be expected to cause enhancement of the pharmacological side effects mentioned above. Observations in animals show that extreme overdosage (100 - 200 times recommended daily dose) may produce estrogenic effects.

There have been reports in the literature that tamoxifen given at several times the standard dose may be associated with prolongation of the QT interval of the ECG.

There is no specific antidote to overdosage, and treatment must be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents; Anti-estrogens
ATC code: L02BA01

Mechanism of action and pharmacodynamic effects:

Tamoxifen is a non-steroidal, triphenylethylene-based drug, which displays a complex spectrum of estrogen antagonist and estrogen agonist-like pharmacological effects in different tissues. In breast cancer patients, at the tumor level, tamoxifen acts primarily as an antiestrogen, preventing estrogen binding to the estrogen receptor. Adjuvant treatment with tamoxifen for 5 years in women having breast cancer with estrogen receptor-positive or unknown receptor status has been shown to have a significantly greater effect than 1 or 2 years of treatment, significantly reducing disease recurrence

and increasing 10-year survival. These benefits were mostly independent of age, menopausal status, tamoxifen dose, and additional chemotherapy. In the clinical situation, it is recognized that tamoxifen leads to reductions in levels of blood total cholesterol and low-density lipoproteins in postmenopausal women of the order of 10 - 20%. In addition, tamoxifen has also been reported to maintain bone mineral density in postmenopausal women.

An uncontrolled trial was undertaken in a heterogeneous group of 28 girls aged 2 to 10 years with McCune Albright Syndrome (MAS), who received 20 mg once a day for up to 12 months duration. Of the patients who reported vaginal bleeding during the pre-study period, 62% (13 of 21 patients) reported no bleeding for 6 months and 33% (7 of 21 patients) reported no vaginal bleeding for 12 months. Mean uterine volume increased after 6 months of treatment and doubled at the end of the one-year study. As these findings are consistent with the pharmacodynamic properties of tamoxifen, a causal relationship cannot be established.

CYP2D6 polymorphism status may be associated with variability in clinical response to tamoxifen. The poor metabolizer status may be associated with reduced response. The consequences of the findings for the treatment of CYP2D6 poor metabolizers have not been fully elucidated (see Section 4.4 Special warnings and precautions for use, 4.5 Interaction with other medicinal products and other forms of interaction and 5.2 Pharmacokinetic properties).

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.

5.2 Pharmacokinetic properties

Absorption:

After oral administration, tamoxifen is absorbed rapidly with maximum serum concentrations attained within 4–7 hours. Steady state concentrations (about 300ng/ml) are achieved after four weeks treatment with 40mg daily.

Distribution:

The drug is highly bound to serum albumin (>99%).

Biotransformation:

Metabolism is by hydroxylation, demethylation and conjugation, giving rise to several metabolites, which have a similar pharmacological profile to the parent compound and thus contribute to the therapeutic effect.

Tamoxifen is metabolized mainly via CYP3A4 to N-desmethyl-tamoxifen, which is further metabolized by CYP2D6 to another active metabolite endoxifen. In patients who lack the enzyme CYP2D6 endoxifen concentrations are approximately 75% lower than in patients with normal CYP2D6 activity. Administration of strong CYP2D6 inhibitors reduces circulating endoxifen levels to a similar extent.

Elimination:

Excretion occurs primarily via the feces. An elimination half-life of approximately 7 days has been calculated for the drug itself, whereas that for N-desmethyltamoxifen, the principal circulating metabolite, is 14 days.

Patient characteristics:

Age

In a clinical study where girls between 2 and 10 years with McCune Albright Syndrome (MAS) received 20mg tamoxifen once a day 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.

5.3 Preclinical safety data

Tamoxifen was not mutagenic in a range of *in-vitro* and *in-vivo* mutagenicity tests. Tamoxifen was genotoxic in some *in-vitro* and *in-vivo* genotoxicity tests in rodents. Gonadal tumors in mice and liver tumors in rats receiving tamoxifen have been reported in long-term studies. The clinical relevance of these findings has not been established.

Reproductive toxicology studies in rats, rabbits and monkeys have shown no teratogenic potential. Tamoxifen was associated with changes similar to those caused by estradiol, ethinylestradiol, clomiphene and diethylstilbestrol (DES).

6. PHARMACEUTICAL PARTICULARS

6.1 Excipients

Lactose (derived from bovine milk)
Maize starch
Pregelatinized cornstarch
Magnesium stearate
Film coating:
Methylhydroxypropylcellulose (E5)
Propylene glycol
Opaspray White M-1-711B (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at room temperature below 25°C, protected from light and humidity.

6.5 Nature and contents of container

Blister packs of white PVC and aluminum foil, coated with PVC/PVDC film, containing 30 tablets.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İstanbul / TÜRKİYE

8. MARKETING AUTHORISATION NUMBER(S)

2017/823

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF AUTHORIZATION

Date of first authorization : 25.10.2017
Date of renewal of authorization :

10. DATE OF REVISION OF THE TEXT