SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
VERIDEX 1 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance:
Anastrozole 1mg
Excipients:
Lactose monohydrate (from cow's milk) ..... 16 mg
Lactose anhydrous (from cow's milk) ..... 16 mg
For the list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
White, round, biconvex, flat on both sides, film coated tablets without scores

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
VERIDEX is used for
- treatment of early stage breast cancer in hormone-receptor positive postmenopausal women,
- treatment of advanced stage breast cancer in postmenopausal women.

Efficacy has not been demonstrated in patients who are estrogen receptor negative except those who have previously shown a positive clinical response to tamoxifen.

4.2. Posology and method of administration
Posology/frequency and duration of administration
Adults (including the elderly): 1 mg once a day orally.
The treatment is advised to be continued for 5 years in early stage breast cancer.

Method of administration
For oral use.

Additional information for special populations
Renal/Hepatic impairment:
No dose change is recommended in mild or moderate renal impairment.
No dose change is recommended in mild hepatic impairment.

Pediatric population:
It is not recommended to be used in children (see Sections 4.4, 5.1 and 5.2).

Geriatric population
No dose change is recommended in the elderly.

4.3. Contraindications
VERIDEX is contraindicated in:
- Premenopausal women
- Pregnancy and lactation
- Patients with severe renal dysfunction (creatinine clearance <30 ml/min)

- Patients with moderate or severe liver dysfunction
- Patients with hypersensitivity to anastrozole or any ingredients contained in the formulation of VERIDEX (see Section 6.1)

4.4. Special warnings and precautions for use

Since the safety and efficacy of VERIDEX in children has not been proved, it is not recommended to be used in children (see Sections 5.1 and 5.2).

Tamoxifen and other estrogen-containing treatments should not be administered concomitantly with VERIDEX, as they will eliminate the pharmacological effect of VERIDEX (see Sections 4.5 and 5.1). VERIDEX should not be used in premenopausal women. If in doubt, menopause should be confirmed by laboratory tests (luteinizing hormone [LH], follicle-stimulating hormone [FSH] and/or estradiol levels) before treatment.

No data is present to support safety use of VERIDEX in patients with moderate or severe hepatic impairment or severe renal impairment (creatinine clearance <30 ml/min).

There are no data on the use of anastrozole with LHRH analogues. This combination should not be used outside of clinical studies.

Since VERIDEX reduces circulating estrogen levels, this may lead to an increased risk of fractures due to decreased bone mineral density (see Section 4.8). Women with osteoporosis or at risk of osteoporosis should have their bone mineral density assessed at the start of treatment and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored. It should be noted that the use of bisphosphonates in postmenopausal women may stop further bone mineral loss that may be caused by anastrozole (see Section 4.8).

This medicinal 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

Anastrozole inhibits CYP 1A2, 2C8/9, and 3A4 *in vitro*. Clinical studies with antipyrine and warfarin indicate that 1 mg anastrozole does not significantly inhibit the metabolism of antipyrine and R- and S-warfarin, including that concomitant use of anastrozole with other drugs is not expected to cause clinically significant drug interactions via cytochrome P 450.

Enzymes that mediate the metabolism of anastrozole have not been identified. Cimetidine, a nonspecific inhibitor of CYP enzymes, does not affect the plasma concentrations of anastrozole. The effect of potent CYP inhibitors is unknown.

A review of clinical trial safety data revealed no clinically significant interactions in patients receiving other commonly used medications concomitantly with anastrozole. No clinically significant interactions with bisphosphonates (see Section 5.1).

Tamoxifen and other estrogen-containing treatments should not be administered concomitantly with VERIDEX, as they will eliminate the pharmacological effect of VERIDEX (see Section 4.4).

4.6. Fertility, pregnancy and lactation
General recommendation
Pregnancy category: X.

Women of childbearing potential/Birth control (Contraception)
It should not be administered in premenopausal women as it is contraindicated.

Pregnancy
VERIDEX is contraindicated during pregnancy (see Section 4.3).

Lactation
VERIDEX is contraindicated in breast-feeding women (see Section 4.3).

Reproduction ability/Fertility
The effects of anastrozole on fertility in humans have not been studied. Studies in animals have shown reproductive toxicity (see Section 5.3).

4.7. Effects on ability to drive and use machines
VERIDEX does not decrease the ability to drive and use machinery. However, since asthenia and somnolence have been reported with use of anastrozole, patients should be careful, if such symptoms develop while driving or using machinery.

4.8. Undesirable effects
Unless specified, the following frequency categories were calculated from adverse events reported in a large 5-year phase III study (the Anastrozole Tamoxifen Alone and in Combination (ATAC) study) in 9,366 postmenopausal women with operable breast cancer.

Adverse drug reactions are listed according to the frequencies 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), unknown ((cannot be estimated from available data). The most frequently reported are headache, hot flushes, nausea, rash, arthralgia, and joint stiffness.

Adverse reactions by System Organ Class and frequency		
Metabolism and nutrition disorders	Common	Anorexia Hypercholesterolemia
	Uncommon	Hypercalcemia (with or without increase in parathyroid hormone)
Nervous system disorders	Very common	Headache
	Common	Somnolence Carpal tunnel syndrome* Sensory disturbances (including paresthesia, taste loss and taste disorders)
Vascular disorders	Very common	Hot flushes
Gastrointestinal disorders	Very common	Nausea
	Common	Diarrhea Vomiting

Hepatobiliary diseases	Common	Increased levels of alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase
	Uncommon	Increased levels of gamma-GT and bilirubin, hepatitis
Skin and subcutaneous tissue disorders	Very common	Rash
	Common	Hair thinning (alopecia) Allergic reactions
	Uncommon	Urticaria
	Rare	Erythema multiforme, anaphylactoid reactions, cutaneous vasculitis (Henoch-Schönlein Purpura)**
	Very rare	Stevens-Johnson syndrome, angioedema
Musculoskeletal, connective tissue and bone disorders	Very common	Arthralgia/joint stiffness, arthritis, osteoporosis
	Common	Bone pain, myalgia
	Uncommon	Trigger finger
Reproductive system and breast disorders	Common	Vaginal dryness, Vaginal bleeding***
General disorders and administration site conditions	Very common	Asthenia

*Carpal Tunnel Syndrome events were reported in clinical trials in more patients treated with anastrozole than in patients receiving tamoxifen. However, the majority of these events occurred in patients with identifiable risk factors for developing this condition.
**Since cutaneous vasculitis and Henoch-Schönlein purpura were not observed in ATAC, the frequency category of these events can be considered “Rare” (≥0.01% and <0.1%) based on the worst value of the point estimate.
***Vaginal bleeding has been reported commonly in the first few weeks after switching to anastrozole from hormone treatment in patients with advanced stage breast cancer who have received a hormonal therapy previously. If bleeding persists, an advanced evaluation should be considered.

Since VERIDEX reduces circulating estrogen levels, bone mineral density may be reduced, which may lead to an increased risk of bone fractures in some patients (see Section 4.4 Special warnings and precautions for use).

The table below shows the frequencies of pre-specified adverse events in the ATAC study that occurred during study treatment and within 14 days of stopping treatment, without establishing a causal relationship to anastrozole use.

Adverse effects	**Anastrozole (N=3092)**	**Tamoxifen (N=3094)**
Hot flushes	1104 (35.7%)	1264 (40.9%)
Joint pain/stiffness	1100 (35.6%)	911 (29.4%)
Mood disorders	597 (19.3%)	554 (17.9%)
Exhaustion/asthenia	575 (18.6%)	544 (17.6%)

Nausea and vomiting	393 (12.7%)	384 (12.4%)
Fractures	315 (10.2%)	209 (6.8%)
Spine. hip or wrist/Colles fractures	133 (4.3%)	91 (2.9%)
Wrist/Colles fractures	67 (2.2%)	50 (1.6%)
Spinal fractures	43 (1.4%)	22 (0.7%)
Hip fractures	28 (0.9%)	26 (0.8%)
Cataract	182 (5.9%)	213 (6.9%)
Vaginal bleeding	167 (5.4%)	317 (10.2%)
Ischemic cardiovascular disease	127 (4.1%)	104 (3.4%)
Angina pectoris	71 (2.3%)	51 (1.6%)
Myocardial infarction	37 (1.2%)	34 (1.1%)
Coronary artery disease	25 (0.8%)	23 (0.7%)
Myocardial ischemia	22 (0.7%)	14 (0.5%)
Vaginal discharge	109 (3.5%)	408 (13.2%)
Any venous thromboembolic event	87 (2.8%)	140 (4.5%)
Deep venous thromboembolic events, including pulmonary embolism	48 (1.6%)	74 (2.4%)
Ischemic cerebrovascular events	62 (2%)	88(2.8%)
Endometrial cancer	4 (0.2%)	13 (0.6%)

After a median follow-up of 68 months, 22 and 15 fractures per 1000 patient-years were observed in the anastrozole and tamoxifen groups, respectively. The rate observed with anastrozole is within the range reported in age-matched postmenopausal populations. The incidence of osteoporosis was 10.5% in patients treated with anastrozole and 7.3% in patients treated with tamoxifen.

It has not been determined whether the rates of fractures and osteoporosis seen in patients receiving anastrozole in the ATAC study reflect a protective effect of tamoxifen, a specific effect of anastrozole, or both.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is essential. It allows continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose

There is limited clinical experience about accidental overdose. In animal studies, anastrozole has shown low acute toxicity. Clinical studies have been conducted with various doses of anastrozole and a single dose up to 60 mg in healthy male volunteers and a dose up to 10 mg daily in postmenopausal women with advanced breast cancer has been tolerated well. No single dose of anastrozole causing life-threatening symptoms has been determined. It has no specific antidote and treatment should be symptomatic.

In overdose, possibility of usage of several different drugs should be considered. If the patient is awake, vomiting may be stimulated. Since anastrozole is not bound to protein with a high rate, dialysis may be beneficial. General supportive treatment should be performed including close monitoring of the patient and frequent measurement of vital signs.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Enzyme inhibitors
ATC Code: L02BG03

Anastrozole is a strong and highly selective nonsteroidal aromatase inhibitor. In postmenopausal women, estradiol is formed by transformation of androstenedione to estrone by aromatase enzyme complex mainly in peripheral tissues. Afterwards estrone is converted to estradiol. It has been shown that decreased circulatory estradiol levels have a beneficial effect in women with breast cancer. Anastrozole administered at a dose of 1 mg daily to postmenopausal women has been shown to suppress estradiol by more than 80% using highly sensitive methods.

Anastrozole has no progestogenic, androgenic or estrogenic activity.

Measurement by adrenocorticotrophic hormone (ACTH) test before or after administration of anastrozole has showed that doses up to 10 mg daily has no effect on cortisol or aldosterone secretion. Therefore, additional corticoids are not required.

Primary adjuvant therapy in early stage breast cancer
In a large phase III study of 9366 postmenopausal women with operable breast cancer, anastrozole was shown to provide statistically superior disease-free survival to tamoxifen when used for 5 years. In a prospectively determined hormone receptor-positive population, anastrozole was observed to be more effective than tamoxifen in terms of disease-free survival.

The time to recurrence with anastrozole was found to be statistically significantly longer than with tamoxifen. This difference in favor of anastrozole was seen to be greater than the existing difference in disease-free survival in both the ITT (Intention To Treat) population and the hormone receptor-positive population.

The time to development of distant metastases with anastrozole is statistically significantly longer than with tamoxifen.

The incidence of contralateral breast cancer statistically significantly decreased with anastrozole compared to tamoxifen.

After 5 years of continued treatment, anastrozole is at least as effective as tamoxifen in terms of overall survival. However, due to the low mortality rates, additional follow-up periods are needed to more clearly establish the long-term survival associated with anastrozole compared with tamoxifen. With a median follow-up of 68 months, ATAC study patients have not been followed for a sufficient period after 5 years of treatment to compare the long-term post-treatment effects of anastrozole with tamoxifen.

ATAC endpoint summary: 5-year treatment completion analysis

Efficacy endpoint	Number of events (frequency)			
	ITT population		Hormone receptor-positive tumor status	
	Anastrozole (N=3125)	Tamoxifen (N=3116)	Anastrozole (N=2618)	Tamoxifen (N=2598)
Disease-free survival[a]	**575 (18.4)**	**651 (20.9)**	**424 (16.2)**	**497 (19.1)**
Relative risk	0.87		0.83	
2-Sided 95% confidence interval	0.78-0.97		0.73-0.94	
p-value	0.0127		0.0049	
Distant disease-free survival[b]	**500 (16)**	**530 (17)**	**370 (14.1)**	**394 (15.2)**
Relative risk	0.94		0.93	
2-Sided 95% confidence interval	0.83-1.06		0.8-1.07	
p-value	0.285		0.2838	
Time to recurrence[c]	**402 (12.9)**	**498 (16)**	**282 (10.8)**	**370 (14.2)**
Relative risk	0.79		0.74	
2-Sided 95% confidence interval	0.7-0.9		0.64-0.87	
p-value	0.0005		0.0002	
Time to distant recurrence	**324 (10.4)**	**375 (12)**	**226 (8.6)**	**265 (10.2)**
Relative risk	0.86		0.84	
2-Sided 95% confidence interval	0.74-0.99		0.7-1	
p-value	0.0427		0.0559	
Development of primary cancer in the	**35(1.1)**	**59(1.9)**	**26 (1)**	**54(2.1)**
Probability ratio	0.59		0.47	
2-Sided 95% confidence interval	0.39-0.89		0.3-0.76	
p-value	0.0131		0.0018	
Overall survival[c]	**411 (13.2)**	**420 (13.5)**	**296 (11.3)**	**301 (11.6)**
Relative risk	0.97		0.97	
2-Sided 95% confidence interval	0.85-1.12		0.83-1.14	
p-value	0.7142		0.7339	

[a] Disease-free survival includes all recurrences and is the time until the first occurrence of loco-regional recurrences, new breast cancer in the contralateral breast, or distant recurrences, or death (from any cause).
[b] Distant disease-free survival is the time until the first occurrence of distant recurrence or death (from any cause).
[c] Time until recurrence occurs is the time until the first appearance of loco-regional recurrences, new breast cancer development in the contralateral breast, distant recurrences, or death (due to breast cancer).

[d] Time to distant recurrence is the time until the first occurrence of distant recurrence or death (due to breast cancer).
[e] Number of patients who died (percentage).

As with all decisions about treatment, the relative benefits and risks of the treatment should be evaluated together by the woman with breast cancer and her doctor.

When anastrozole were co-administered with tamoxifen, it was found to be similar to tamoxifen administered alone in terms of efficacy and safety, independently from hormone receptor state.

Adjuvant treatment of patients with hormone-receptor positive early invasive breast cancer treated with adjuvant tamoxifen
In a phase III study (Austrian Breast and Colorectal Cancer Study Group (ABCSG) 8) in 2579 postmenopausal women with hormone receptor-positive early-stage breast cancer who had undergone surgery, radiotherapy or no chemotherapy, and 2 years of adjuvant tamoxifen therapy, disease-free survival was greater in women who stopped taking tamoxifen and started taking anastrozole than in women who continued taking tamoxifen after a median follow-up of 24 months.

Time to any recurrence, time to local or distant metastasis, and time to distant metastasis confirmed that anastrozole had a statistically significant advantage, parallel to disease-free survival results. The incidence of contralateral breast cancer was very low in both groups, with anastrozole having a numerical advantage. Overall survival was similar in the two treatment groups.

Study ABCSG 8 endpoints and summary of results

Efficacy endpoint	**Number of events (frequency)**	
	Anastrozole (N=1297)	**Tamoxifen (N=1282)**
Disease-free survival	65 (5)	93 (7.3)
Relative risk	0.67	
2-Sided 95% confidence interval	0.49-0.92	
p-value	0.014	
Time to any recurrence	36 (2.8)	66 (5.1)
Relative risk	0.53	
2-Sided 95% confidence interval	0.35-0.79	
p-value	0.002	
Time to distant recurrence	22 (1.7)	41 (3.2)
Relative risk	0.52	
2-Sided 95% confidence interval	0.31-0.88	
p-value	0.015	
Development of primary cancer in the contralateral breast	7 (0.5)	15(1.2)
Probability ratio	0.46	
2-Sided 95% confidence interval	0.19-1.13	

p-value	0.09	
Overall survival	43 (3.3)	45 (3.5)
Relative risk	0.96	
2-Sided 95% confidence interval	0.63-1.46	
p-value	0.84	

Combined analysis of two other similar studies with anastrozole (GABG/ARNO 95 and ITA) and the ABCSG 8 and GABG/ARNO 95 studies supports these results.

The safety profile of anastrozole in these 3 studies is consistent with its known safety profile in women with hormone receptor-positive early-stage breast cancer.

Bone Mineral Density (BMD)
Bisphosphonate risedronate vs anastrozole study (SABRE)
In the Phase III/IV SABRE study, 234 postmenopausal women with hormone receptor-positive early-stage breast cancer were classified into low-, intermediate-, and high-risk groups based on their current risk of fragility fractures and were treated with 1 mg/day anastrozole. The primary efficacy parameter was analysis of lumbar spine bone density using DEXA scanning. All patients received treatment with vitamin D and calcium. Patients in the low-risk group (n=42) received anastrozole alone, patients in the intermediate-risk group were randomized to receive anastrozole and risedronate 35 mg once weekly (n=77) or anastrozole and placebo (n=77), and those in the high-risk group received anastrozole and risedronate 35 mg once weekly (n=38). The primary endpoint was change from baseline in lumbar spine bone mass density at 12 months.

The 12-month main analysis showed that patients at moderate and high risk of fragility fractures did not experience a decrease in bone mass density when treated with risedronate 35 mg once weekly in combination with anastrozole 1 mg/day. (As assessed by lumbar spine bone mineral density using DEXA scanning) Additionally, a statistically non-significant decrease in BMD was observed in the low-risk group treated with anastrozole 1 mg/day alone. These findings were reflected in the secondary efficacy variable, change from baseline in total hip bone mineral density at 12 months.

This study provides evidence for the use of bisphosphonates for possible bone mineral loss in postmenopausal women with early-stage breast cancer who were scheduled for treatment with anastrozole.

Pediatric patients
Three clinical studies were conducted in pediatric patients. (2 in pubertal boys with gynecomastia and 1 in girls with McCune-Albright Syndrome)

Gynecomastia studies
Study 006 was a randomized, double-blind, multicenter study in which 82 pubertal males (ages 11 to 18 years) with gynecomastia of greater than 12 months were treated with anastrozole 1 mg/day or placebo daily for up to 6 months. At 6 months of treatment, no significant difference was observed in the number of patients with 50% or greater total breast volume reduction between the Anastrozole 1 mg group and the placebo group.

Study 001 was an open-label, multiple-dose pharmacokinetic study of anastrozole 1 mg daily in 36 pubertal males with gynecomastia of < 12 months duration. Secondary objectives evaluate patient

tolerability and safety and the proportion of patients with at least 50% reduction in the calculated volume of gynecomastia in both breasts from baseline between day 1 of treatment and 6 months after baseline.

In this study, a pharmacodynamic subpopulation of 25 boys was selected to investigate the potential benefits of anastrozole. Patients had a 50% or greater decrease in total breast volume at 6 months, 55.6% when measured by ultrasound and 77.8% when measured by caliper. (observational data only, no statistical analysis was performed on these results)

McCune-Albright Syndrome study
Study 0046 was an international, multicenter, open-label investigational study in 28 girls (age 2 to ≤10) with McCune Albright syndrome (MAS). The primary objective was to evaluate the safety and efficacy of treatment with anastrozole 1 mg/day in patients with MAS. The effectiveness of the study treatment was based on the proportion of patients who fully met the defined criteria for vaginal bleeding, bone age, and growth velocity.

No statistically significant change in vaginal bleeding day frequency was observed during treatment. There is no clinically important change in Tanner staging, mean ovarian volume, or mean uterine volume. No statistically significant change in the rate of bone age increase was observed during treatment compared with the baseline. Growth velocity (cm/year) decreased significantly between 0th and 12th months before treatment and during the 2nd 6-month period (between 7th and 12th months) before the treatment ($p<0.05$). Among patients with baseline vaginal bleeding, 28% had a 50% or greater reduction in the frequency of bleeding days during treatment; 40% had cessation of bleeding over a 6-month period; and 12% had cessation of bleeding over a 12-month period.

When the overall evaluation of adverse events in children under 18 years of age is made, no opinion can be made regarding safety and tolerability.

5.2. Pharmacokinetic properties

Absorption
Absorption of anastrozole is rapid. The small change in absorption rate is not expected to produce clinically significant effects at steady-state plasma concentration. Food slightly reduces the rate of absorption but does not prolong it.

Distribution:
Maximum plasma concentrations typically occur within two hours after dosing (fasting). Steady-state plasma concentrations of anastrozole are reached after dose administration for 7 days in 90-95% patients. There is no evidence indicating any relations between pharmacokinetic parameters of anastrozole are time- or dose-dependent. Only 40% of anastrozole binds to plasma proteins.

Biotransformation
The metabolism of anastrozole consists of N-dealkylation, hydroxylation and glucuronidation.

Elimination
Anastrozole is eliminated slowly. Plasma elimination half-life is approximately 40-50 hours. In postmenopausal women, anastrozole is extensively metabolized, with less than 10% of anastrozole excreted unchanged in the urine within 72 hours. Its metabolites are excreted primarily in urine. The most important metabolite in plasma (triazole) does not inhibit aromatase enzyme.

Patient characteristics

Gender
Not applicable.

Elderly
In postmenopausal women, the pharmacokinetics of anastrozole are not age-dependent.

Pediatric patients
Pharmacokinetic studies have not been conducted in children.

Renal impairment
Oral clearance of anastrozole in volunteers with renal impairment was similar to that observed in healthy volunteers.

Hepatic impairment
Oral clearance of anastrozole in volunteers with stable hepatic cirrhosis was similar to that observed in healthy volunteers.

5.3. Preclinical safety data

Acute Toxicity
In acute toxicity studies in rodents, the median lethal dose administered orally was greater than 100 mg/kg/day and the median lethal dose administered intraperitoneally was greater than 50 mg/kg/day. In an oral acute toxicity study in the dog, the median lethal dose was greater than 45 mg/kg/day.

Chronic Toxicity
Multiple-dose toxicity studies were performed in rats and dogs. No effect levels of anastrozole were detected in toxicity studies. The effects observed at low (1 mg/kg/day) and medium doses (dog 3 mg/kg/day and rat 5 mg/kg/day) were due to the pharmacological or enzyme induction properties of anastrozole and were not associated with significant toxic or degenerative changes.

Mutagenicity
Genetic toxicology studies have shown that anastrozole is not mutagenic or clastogenic.

Reproductive Toxicology
In a fertility study, newly weaned male rats were given 50 or 400 mg/l of anastrozole via drinking water for 10 weeks. Mean plasma concentrations were measured as 44.4 (± 14.7) ng/ml and 165 (± 90) ng/ml, respectively. Mating indices were adversely affected in both dose groups, with reduced fertility being evident only at the 400 mg/l dose level. The decrease was transient as all mating and fertility parameters were similar to control group values after a 9-week treatment-free recovery period.

Oral administration of 1 mg/kg/day anastrozole to female rats caused an increase in the incidence of infertility and administration of 0.02 mg/kg/day caused pre-implantation loss. These effects occurred at clinically relevant doses. The impact on humans cannot be excluded. These effects are related to the pharmacology of the compound and are completely reversible after 5 weeks of withdrawal of the compound.

No teratogenic effects were observed following administration of 1 and 0.2 mg/kg/day anastrozole to pregnant rats and rabbits, respectively. The effects observed (placental expansion in rats and failure

to conceive in rabbits) are related to the pharmacology of the compound.

The lives of the offspring of rats given anastrozole at doses of 0.02 mg/kg/day or more, starting from the 17th day of pregnancy until the 22nd day after birth, were in danger. These effects are related to the pharmacological effect of the compound on parturition. Maternal anastrozole treatment did not produce any adverse effects that could affect the behavior or reproductive performance of the offspring.

Carcinogenicity
A two-year oncogenicity study in rats resulted in an increased incidence of hepatic neoplasms and uterine stromal polyps in females and thyroid adenomas in males only at the high dose (25 mg/kg/day). These changes occurred at a dose that represents 100 times the therapeutic human exposure and are not considered clinically relevant to the anastrozole treatment administered to patients.

A two-year oncogenicity study in mice resulted in the induction of benign ovarian tumors and altered incidences of lymphoreticular neoplasms (lower numbers of histiocytic sarcomas in females, more deaths from lymphoma). These changes are thought to be specific aromatase inhibition effects in mice and have no clinical relevance to anastrozole treatment in patients.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate (from cow's milk)
Lactose anhydrous (from cow's milk)
Sodium starch glycolate
Microcrystalline cellulose (Avicel PH-102)
Colloidal silicon dioxide (Anyhdrous)
Magnesium stearate
Opadry 04F58804 White (film coating):
Hypromellose E464
Titanium dioxide E171
Macrogol E1621

6.2. Incompatibilities

There are no known incompatibilities.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at room temperature below 25°C.

6.5. Nature and contents of container

Each cardboard box contains 28 film coated tablets in PVC Alu blister packs.

6.6. Special precautions for disposal and other handling

Any unused medicinal products or waste materials should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

Deva Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad.
34303 No:1 Küçükçekmece/İSTANBUL/TÜRKİYE
Phone: +90212 692 92 92
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8. MARKETING AUTHORIZATION NUMBER

247/10

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Date of first authorization: 24.12.2012
Latest renewal of authorization:

10. DATE OF REVISION OF THE TEXT