SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Anastrozole Denk 1 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: anastrozole
Each film-coated tablet contains 1 mg anastrozole.

Excipient with known effect:
Each film-coated tablet contains 90 mg of lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White to off-white, round, biconvex film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Anastrozole Denk 1 mg is indicated for the:
- treatment of hormone receptor-positive, advanced breast cancer in postmenopausal women.
- adjuvant treatment of hormone receptor-positive, early invasive breast cancer in postmenopausal women.
- adjuvant treatment of hormone receptor-positive, early invasive breast cancer in postmenopausal women already receiving adjuvant tamoxifen for 2 to 3 years.

4.2 Posology and method of administration

Posology
The recommended dose of Anastrozole Denk 1 mg for adults including elderly patients is 1 mg tablet once daily.

For postmenopausal women with hormone receptor-positive, early invasive breast cancer, the recommended duration of adjuvant endocrine therapy is 5 years.

Special patient groups

Paediatric population
Anastrozole Denk 1 mg is not recommended for use in children and adolescents due to insufficient data on safety and efficacy (see sections 4.4 and 5.1).

Impaired renal function
No dose modification is recommended for patients with mild or moderate renal impairment. Anastrozole Denk 1 mg should be used with caution in patients with severe renal impairment (see sections 4.4 and 5.2).

Impaired hepatic function

No dose modification is recommended for patients with mild hepatic impairment. Caution is advised in patients with moderate to severe hepatic impairment (see section 4.4).

Method of administration
Anastrozole Denk 1 mg is taken orally.

4.3 Contraindications

Anastrozole Denk 1 mg is contraindicated in:
- pregnant or breastfeeding women.
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General
Anastrozole Denk 1 mg should not be used in premenopausal women. Menopause should be demonstrated biochemically (lutein-forming hormone [LH], follicle-stimulating hormone [FSH] and/or oestradiol plasmas levels) in all patients whose menopausal status is not clear. There are no data that support the use of Anastrozole Denk 1 mg with LHRH analogues.

Concomitant use of tamoxifen or oestrogen-containing medicinal products and Anastrozole Denk 1 mg should be avoided, as this may reduce the pharmacological effect of Anastrozole Denk 1 mg (see section 4.5 and 5.1).

Effects on bone density
Because anastrozole reduces endogenous oestrogen plasma levels, Anastrozole Denk 1 mg may induce a reduction in bone density and a possible associated increased risk of fracture (see section 4.8).

Women with osteoporosis or at increased risk of osteoporosis should have their bone density checked at the start of treatment and at regular intervals during treatment. If indicated, osteoporosis treatment or prophylaxis should be initiated and carefully monitored. The use of specific treatments, e.g. bisphosphonates, may possibly prevent further anastrozole-induced loss of bone density in postmenopausal women and could be considered (see section 4.8).

Impaired hepatic function
Anastrozole has not been investigated in breast cancer patients with moderate or severe hepatic impairment. Anastrozole exposure may be increased in patients with hepatic impairment (see section 5.2); Anastrozole Denk 1 mg should be used with caution in patients with moderate to severe hepatic impairment (see section 4.2). Treatment should be based on a benefit/risk assessment for each individual patient.

Impaired renal function
Anastrozole has not been studied in breast cancer patients with severe renal impairment. Anastrozole exposure is not increased in subjects with severe renal impairment (GFR<30 mL/min, see section 5.2); Anastrozole Denk 1 mg should be used with caution in patients with severe renal impairment (see section 4.2).

Paediatric population
Anastrozole Denk 1 mg is not recommended for use in children and adolescents, as safety and efficacy in this patient group have not been established (see section 5.1).

In boys with growth hormone deficiency, Anastrozole Denk 1 mg should not be used in addition to growth hormone treatment. In the pivotal clinical study, efficacy was not shown and safety was not demonstrated (see section 5.1). As anastrozole lowers oestradiol plasma levels, Anastrozole Denk 1 mg must not be used in girls with growth hormone deficiency in addition to growth hormone treatment. No long-term data are available on safety in children and adolescents.

Lactose

As the tablets contain lactose, this product is not recommended for patients with rare hereditary problems of galactose intolerance, of severe lactose deficiency or of glucose-galactose.

4.5 Interaction with other medicinal products and other forms of interaction

Anastrozole inhibits CYP1A2, 2C8/9 and 3A4 *in vitro*. Clinical studies with phenazone and warfarin have shown that anastrozole, at a dosage of 1 mg, does not significantly inhibit the metabolism of phenazone and R- and S-warfarin. This suggests that clinically relevant drug interactions mediated by CYP enzymes are unlikely with concomitant use of Anastrozole Denk 1 mg and other medicinal products.

The enzymes involved in the metabolism of anastrozole have not been identified. Cimetidine, a weak, non-specific inhibitor of CYP enzymes, did not affect the plasma concentrations of anastrozole. The effect of potent CYP inhibitors is not known.

A review of the clinical trial safety database revealed no indications of any clinically significant interaction in patients treated with Anastrozole Denk 1 mg also receiving other commonly prescribed medicines. There were no clinically significant interactions with bisphosphonates (see section 5.1).

Concomitant use of tamoxifen or oestrogen-containing medicines and Anastrozole Denk 1 mg should be avoided, as this may reduce the pharmacological effect of Anastrozole Denk 1 mg (see section 4.4 and 5.1).

4.6 Fertility, pregnancy and breastfeeding

Pregnancy
To date, there is no experience with the use of anastrozole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Anastrozole Denk 1 mg is contraindicated during pregnancy (see section 4.3).

Breastfeeding
To date, there is no experience with the use of anastrozole during breastfeeding. Anastrozole Denk 1 mg is contraindicated during breastfeeding (see section 4.3).

Fertility
The effects of anastrozole on human fertility 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

Anastrozole Denk 1 mg has no or negligible influence on the ability to drive and use machines. However, asthenia and somnolence have been reported with use of anastrozole, and as long as these symptoms persist, caution should be exercised when driving or using machines.

4.8 Undesirable effects

The following table shows adverse reactions that have occurred in clinical studies, in post-marketing studies or as spontaneous reports. Unless otherwise stated, the frequencies were calculated on the basis of adverse reactions reported within the framework a large phase III study, conducted in 9,366 postmenopausal women with operable breast cancer receiving adjuvant treatment over 5 years (the *Arimidex, Tamoxifen, Alone or in Combination* [ATAC] study).

The adverse reactions listed below have been arranged by frequency and system organ class (SOC). The frequency categories are defined according to the following convention: 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). The most commonly reported adverse reactions were headache, hot flushes, nausea, skin rash, joint pain/stiffness, arthritis and asthenia.

Table 1 Adverse reactions by system organ class and frequency

Adverse reactions by SOC and frequency		
Metabolism and nutrition disorders	Common	Anorexia Hypercholesterolaemia
	Uncommon	Hypercalcaemia (with or without an increase in parathyroid hormone)
Nervous system disorders	Very common	Headache
	Common	Somnolence Carpal tunnel syndrome* Sensory disturbances (including paraesthesia, loss of taste and taste disturbance)
Vascular disorders	Very common	Hot flushes
Gastrointestinal disorders	Very common	Nausea
	Common	Diarrhoea Vomiting
Hepatobiliary disorders	Common	Increase in 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 loss (alopecia) Allergic reactions
	Uncommon	Urticaria
	Rare	Erythema multiforme Anaphylactic reaction Cutaneous vasculitis (including some reports of Schoenlein-Henoch purpura)**
	Very rare	Stevens-Johnson syndrome Angioedema
Musculoskeletal and connective tissue disorders	Very common	Joint pain/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

* In clinical studies, a greater number of cases of carpal tunnel syndrome have been observed in patients treated with anastrozole than in patients treated with tamoxifen. However, the majority of these cases have occurred in patients with identifiable risk factors for the development of this disease.

** Since cutaneous vasculitis and Schoenlein-Henoch purpura have not been observed within the framework of the ATAC study, the frequency category for these events can be considered as "rare" (≥0.01% and <0.1%), based on the worst value of the point estimate.

*** Vaginal bleeding has been commonly reported, especially in patients with advanced breast cancer in the first few weeks after switching from an existing hormone therapy to anastrozole. If bleeding persists, further clarification should be considered.

The following table shows the frequencies of pre-specified adverse events occurring after a mean follow-up period of 68 months as part of the ATAC study, regardless of whether there was a causal link. The adverse events were observed in patients during and up to 14 days after completion of the study therapy.

Table 2 Pre-specified adverse events as part of the ATAC study

Adverse events	Anastrozole (n=3092)	Tamoxifen (n=3094)
Hot flushes	1104 (35.7%)	1264 (40.9%)
Joint pain/stiffness	1100 (35.6%)	911 (29.4%)
Mood lability	597 (19.3%)	554 (17.9%)
Fatigue/asthenia	575 (18.6%)	544 (17.6%)
Nausea and vomiting	393 (12.7%)	384 (12.4%)
Bone fractures	315 (10.2%)	209 (6.8%)
Bone fractures of the spine, hip or wrist/Colles' fractures	133 (4.3%)	91 (2.9%)
Wrist/Colles' fractures	67 (2.2%)	50 (1.6%)
Bone fractures of the spine	43 (1.4%)	22 (0.7%)
Bone fractures of the hip	28 (0.9%)	26 (0.8%)
Cataracts	182 (5.9%)	213 (6.9%)
Vaginal bleeding	167 (5.4%)	317 (10.2%)
Ischaemic 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 heart disease	25 (0.8%)	23 (0.7%)
Myocardial ischaemia	22 (0.7%)	14 (0.5%)
Vaginal discharge	109 (3.5%)	408 (13.2%)
Venous thromboembolisms (total)	87 (2.8%)	140 (4.5%)
Deep vein thrombosis including pulmonary embolism	48 (1.6%)	74 (2.4%)
Ischaemic cerebrovascular events	62 (2.0%)	88 (2.8%)
Endometrial carcinoma	4 (0.2%)	13 (0.6%)

With a mean follow-up time of 68 months, a fracture rate of 22 per 1000 patient-years was observed in the anastrozole group and of 15 per 1000 patient-years in the tamoxifen group. The fracture rate observed for anastrozole is similar to the reference range observed in the postmenopausal population of this same age group. The incidence for the occurrence of osteoporosis was 10.5% in patients treated with anastrozole and 7.3% in patients treated with tamoxifen.

It has not been established whether the fracture and osteoporosis rate observed in patients treated with anastrozole as part of the ATAC study reflects a protective effect of tamoxifen, a specific effect of anastrozole, or both.

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.

4.9 Overdose

There is only limited clinical experience of accidental overdose. In animal trials, the acute toxicity of anastrozole was shown to be low. In clinical studies with anastrozole at various dosages, healthy male subjects received single doses of up to 60 mg and postmenopausal women with advanced breast cancer up to 10 mg daily; these dosages were well tolerated. No single dose of anastrozole resulting in life-threatening symptoms has been determined. There is no specific antidote for overdose and treatment must be symptomatic.

In the treatment of overdose, the possibility that several medicinal products have been ingested must be taken into account. If the patient is conscious, vomiting should be induced. As anastrozole is not highly protein-bound, dialysis may be of benefit. Generally supportive measures, including frequent monitoring of vital signs and close patient monitoring, are indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Enzyme inhibitors, ATC-code: L02B G03

Mechanism of action and pharmacodynamic effects
Anastrozole is a potent, highly selective non-steroidal aromatase inhibitor. In postmenopausal women, oestradiol is mainly formed in the peripheral tissue by an aromatase enzyme complex, with the conversion of androstenedione to oestrone. Subsequently, oestrone is converted to oestradiol. In women with breast cancer, the benefit of reducing circulating oestradiol in plasma has been demonstrated. Using a highly sensitive method, it has been demonstrated that daily administration of 1 mg anastrozole lowers the oestradiol level in postmenopausal women by more than 80%.

Anastrozole has no progestogenic, androgenic or oestrogenic effect.

Measurements before and after a standard stress test for the detection of adrenocorticotropic hormone (ACTH load test) show that doses of up to 10 mg anastrozole per day have no influence on the secretion of cortisol and aldosterone. Corticosteroid replacement is therefore not required.

Clinical efficacy and safety

Advanced breast cancer

First-line therapy in postmenopausal women with advanced breast cancer
In order to investigate the efficacy of anastrozole compared to tamoxifen as first-line therapy for hormone receptor-positive or hormone receptor-unknown, locally advanced or metastatic breast cancer in postmenopausal women, two double-blind, controlled studies with the same design (Study 1033IL/0030 and Study 1033IL/0027) were conducted. A total of 1,021 patients were randomised to receive 1 mg anastrozole once daily or 20 mg tamoxifen once daily. The primary endpoints for both studies were time to tumour progression, objective tumour response rate and safety.

With regard to primary endpoints, Study 1033IL/0030 showed that anastrozole had a statistically significant advantage over tamoxifen with respect to tumour progression (hazard ratio (HR) 1.42, 95% confidence interval (CI) [1.11, 1.82], mean time to progression: 11.1 and 5.6 months for anastrozole and tamoxifen, respectively, p=0.006); objective tumour response rates were the same for anastrozole and tamoxifen. Study 1033 IL/0027 showed that anastrozole and tamoxifen behaved identically with respect to tumour response rates and time to tumour progression. Results for the secondary endpoints supported the results of the primary efficacy endpoints. Within all treatment groups of both studies, too few deaths occurred to draw conclusions about differences in overall survival.

Second-line therapy in postmenopausal women with advanced breast cancer
In two controlled clinical studies (Study 0004 and Study 0005), anastrozole was investigated in postmenopausal women with advanced breast cancer who experienced disease progression after treatment with tamoxifen for either advanced or early breast cancer. A total of 764 patients were randomised to receive either a single daily dose of 1 mg or 10 mg anastrozole, or 40 mg megestrol acetate 4 times daily. Primary efficacy variables were time to progression and objective response rates. The rate of prolonged (more than 24 weeks) disease stability, progression rate and survival time were also calculated. Both studies showed no significant differences between the treatment groups with regard to all efficacy parameters.

Adjuvant treatment of early invasive breast cancer in patients with positive hormone receptor status
In a large phase III study with 9,366 postmenopausal patients with operable breast cancer who had been treated for 5 years (see below), anastrozole was shown to be statistically superior to tamoxifen in terms of disease-free survival. A greater benefit of anastrozole compared to tamoxifen for disease-free survival was observed for a prospectively defined population with positive hormone receptor status.

Table 3 Summary of the endpoints of the ATAC study: final analysis after 5 years of treatment

Study endpoints in terms of efficacy	Number of events (frequency)			
	Intention-to-treat population		Hormone receptor-positive tumour 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)
Hazard ratio	0.87		0.83	
Two-sided 95% confidence interval	0.78 to 0.97		0.73 to 0.94	
p-value	0.0127		0.0049	
Distant metastasis-free survival[b]	500 (16.0)	530 (17.0)	370 (14.1)	394 (15.2)
Hazard ratio	0.94		0.93	
Two-sided 95% confidence interval	0.83 to 1.06		0.80 to 1.07	
p-value	0.2850		0.2838	
Time to disease recurrence[c]	402 (12.9)	498 (16.0)	282 (10.8)	370 (14.2)
Hazard ratio	0.79		0.74	
Two-sided 95% confidence interval	0.70 to 0.90		0.64 to 0.87	
p-value	0.0005		0.0002	
Time to occurrence of distant metastases [d]	324 (10.4)	375 (12.0)	226 (8.6)	265 (10.2)
Hazard ratio	0.86		0.84	
Two-sided 95% confidence interval	0.74 to 0.99		0.70 to 1.00	
p-value	0.0427		0.0559	
Occurrence of primary tumour in the contralateral breast	35 (1.1)	59 (1.9)	26 (1.0)	54 (2.1)
Odds ratio	0.59		0.47	
Two-sided 95% confidence interval	0.39 to 0.89		0.30 to 0.76	
p-value	0.0131		0.0018	
Overall survival time[e]	411 (13.2)	420 (13.5)	296 (11.3)	301 (11.6)
Hazard ratio	0.97		0.97	
Two-sided 95% confidence interval	0.85 to 1.12		0.83 to 1.14	
p-value	0.7142		0.7339	

a Disease-free survival includes all relapses and is defined as the time to first occurrence of local relapse, to first occurrence of contralateral breast cancer, to occurrence of distant metastases or to death (regardless of cause).

b Distant metastasis-free survival is defined as the time to first occurrence of distant metastasis or to death (regardless of cause).

c The time to disease recurrence is defined as the time to first occurrence of locoregional relapse, to first occurrence of contralateral breast cancer, to occurrence of distant metastases or to death due to breast cancer.

d The time to occurrence of distant metastases is defined as the time to first occurrence of distant metastasis or death due to breast cancer.

e Number (%) of deceased patients.

Combination treatment with anastrozole and tamoxifen compared with tamoxifen alone showed no benefit with regard to efficacy in all patients, as well as in the population with positive hormone receptor status. This treatment arm of the study was discontinued.

A long-term comparison as part of an updated mean follow-up period of 10 years showed that the treatment outcomes of anastrozole compared with tamoxifen were consistent with previous analyses.

Adjuvant treatment of early invasive breast cancer in patients with hormone receptor-positive tumour status adjuvantly treated with tamoxifen
A phase III study (Austrian Breast and Colorectal Cancer Study Group [ABCSG] 8) of 2,579 postmenopausal patients with hormone receptor-positive, early breast cancer undergoing surgery with or without radiotherapy, but not chemotherapy (see below), showed that, after a mean follow-up period of 24 months, the switch to Anastrozole Denk 1 mg after 2 years of adjuvant treatment with tamoxifen was statistically superior to further treatment with tamoxifen.

Table 4 Summary of endpoints and results of the ABCSG8 study

Study endpoints with regard to efficacy	Number of events (frequency)	
	Anastrozole (n=1297)	Tamoxifen (n=1282)
Disease-free survival	65 (5.0)	93 (7.3)
Hazard ratio	0.67	
Two-sided 95% confidence interval	0.49 to 0.92	
p-value	0.014	
Time to each relapse	36 (2.8)	66 (5.1)
Hazard ratio	0.53	
Two-sided 95% confidence interval	0.35 to 0.79	
p-value	0.002	
Time to occurrence of distant metastases	22 (1.7)	41 (3.2)
Hazard ratio	0.52	
Two-sided 95% confidence interval	0.31 to 0.88	
p-value	0.015	
Primary tumour in contralateral breast	7 (0.5)	15 (1.2)
Odds ratio	0.46	
Two-sided 95% confidence interval	0.19 to 1.13	
p-value	0.090	
Overall survival	43 (3.3)	45 (3.5)
Hazard ratio	0.96	
Two-sided 95% confidence interval	0.63 to 1.46	
p-value	0.840	

These results were supported by two other similar studies (GABG/ARNO 95 and ITA), in one of which patients underwent surgery and chemotherapy, as well as a combined analysis of ABCSG 8 and GABG/ARNO 95.

The safety profile of Anastrozole Denk 1 mg in these 3 studies was consistent with the established safety profile in postmenopausal patients with hormone receptor-positive, early breast cancer.

Bone density (bone mineral density, BMD)
In the phase III/IV study (Study of Anastrozole with the Bisphosphonate Risedronate [SABRE]), 234 postmenopausal women with hormone receptor-positive, early breast cancer scheduled for treatment with 1 mg anastrozole/day were stratified according to their fracture risk into three groups of low, medium and high risk, respectively. The primary efficacy parameter was the analysis of bone density of the lumbar spine using DEXA scans. All patients received therapy with vitamin D and

calcium. Patients in the low-risk group received anastrozole alone (n=42). Patients in the medium-risk group were randomised to receive either anastrozole plus 35 mg risedronate once weekly (n=77) or anastrozole plus placebo (n=77). Patients in the high-risk group received anastrozole plus 35 mg risedronate once weekly (n=38). The primary endpoint was the deviation from baseline of bone density in the lumbar spine after 12 months.

The main analysis after 12 months has shown that patients already at medium-to-high fracture risk experienced no reduction in bone density when the patients were treated with Anastrozole Denk 1 mg/day in combination with 35 mg risedronate once weekly (determined on the basis of bone density of the lumbar spine using DEXA scans). Furthermore, a statistically non-significant decrease in BMD was observed in the low-risk group treated with Anastrozole Denk 1 mg/day alone. These findings were reflected in the secondary efficacy variable, i.e. the baseline change in overall hip BMD after 12 months.

This study demonstrates that bisphosphonate use could be considered in postmenopausal women with early-stage breast cancer due to be treated with Anastrozole Denk 1 mg, in order to counteract possible loss of bone density.

Paediatric population
Anastrozole Denk 1 mg is not indicated for use in children and adolescents. Efficacy has not been demonstrated in the paediatric patient groups studied (see below). The number of children treated was too low to draw any reliable conclusions regarding safety. No data are available on potential long-term effects of anastrozole treatment in children and adolescents (see also section 5.3).

The European Medicines Agency has waived the obligation to submit the results of studies with anastrozole in one or more subsets of the paediatric population in short stature due to growth hormone deficiency (GHD), testotoxicosis, gynaecomastia and McCune-Albright syndrome (see section 4.2).
Short stature due to growth hormone deficiency
A randomised, double-blind, multicentre study evaluated 52 pubescent boys (aged 11 to 16 years inclusive) with GHD, who were treated with Anastrozole Denk 1 mg/day or placebo in combination with growth hormone over 12 to 36 months. Only 14 participants on anastrozole completed 36 months.

No statistically significant difference to placebo was observed in the growth-related parameters of predicted adult height, height, height SDS (standard deviation score) and growth velocity. No final height data were available. For reliable conclusions on safety, the number of children treated was too low, but an increased fracture rate and a trend towards reduced bone mineral density occurred compared to placebo in the group treated with anastrozole.

Testotoxicosis
An open-label, non-comparative, multicentre study investigated 14 male patients (aged 2 to 9 years) with familial male-limited precocious puberty, also known as testotoxicosis, treated with a combination of anastrozole and bicalutamide. The primary objective was to evaluate the efficacy and safety of this combination treatment over 12 months. Thirteen of the 14 participating patients completed 12 months of combination treatment (one patient was lost to follow-up). After 12 months of treatment, there was no significant difference in growth rate relative to the growth rate during the six months prior to study inclusion.

Gynaecomastia studies
Study 0006 was a randomised, double-blind, multicentre study with 82 pubescent boys (aged 11 to 18 years inclusive) with gynaecomastia of more than 12 months' duration, who were treated for up to 6 months with Anastrozole Denk 1 mg/day or placebo. Between the group treated with Anastrozole Denk 1 mg and the placebo group, there was no significant difference in the number of patients experiencing a 50% or more reduction in total breast volume after 6 months of treatment.

Study 0001 was an open-label, multidose pharmacokinetic study of Anastrozole Denk 1 mg/day in 36 pubescent boys with gynaecomastia of less than 12 months' duration. The secondary objectives were to determine the number of patients with at least a 50% reduction in the volume of

gynaecomastia calculated for both breasts combined, compared to baseline on day 1 and after 6 months with the study therapy, as well as compatibility and safety. After 6 months, a 50% or more decrease in total breast volume was found in 56% (20/36) of these boys.

McCune-Albright syndrome study
Study 0046 was an international, multicentre, open-label exploratory study with anastrozole in 28 girls (aged 2 to ≤ 10 years) with McCune-Albright syndrome (MAS). The primary objective was to evaluate the safety and efficacy of Anastrozole Denk 1 mg/day in patients with MAS. The efficacy of the study medication was measured by the number of patients fulfilling the set criteria with regard to vaginal bleeding, bone age and growth velocity. No statistically significant change was observed in the number of days with vaginal bleeding whilst on therapy. There were no clinically significant changes in Tanner stages, mean ovarian volume or mean uterine volume. No statistically significant change was observed with respect to the increase in bone age with therapy compared to baseline. In relation to the time leading up to treatment, growth velocity (in cm/year) was significantly reduced ($p<0.05$), both for the period from month 0 to month 12 and for the duration of the second 6-month period (from month 7 to month 12).

5.2 Pharmacokinetic properties

Absorption
Absorption of anastrozole occurs rapidly and peak plasma concentrations are usually achieved within 2 hours (in the fasted state). Food leads to a slight delay in the rate of absorption, but does not affect its extent. This slight delay in the absorption rate does not suggest any clinically significant effect on the anastrozole plasma concentration at steady state with once-daily ingestion of anastrozole film-coated tablets. After 7 daily doses, approximately 90 to 95% of anastrozole steady-state plasma concentrations are achieved and accumulation is 3- to 4-fold. There are no indications of any time- or dose-dependency for the pharmacokinetic parameters of anastrozole.

The pharmacokinetics of anastrozole in postmenopausal women is independent of age.

Distribution
The plasma protein binding of anastrozole is only 40%.

Elimination
Anastrozole is eliminated slowly with a plasma elimination half-life of 40 to 50 hours. Anastrozole is extensively metabolised in postmenopausal women, so that less than 10% of the dose is excreted unchanged with the urine within 72 hours. Metabolism of anastrozole occurs via N-dealkylation, hydroxylation and glucuronidation. The metabolites are primarily excreted with the urine. Triazole, the main metabolite in plasma, does not inhibit aromatase.

Impaired renal or hepatic function
In subjects with stable liver cirrhosis, the apparent clearance (CL/F) of anastrozole after oral administration was approximately 30% lower than in a corresponding control group (Study 1033IL/0014). However, the plasma concentrations of anastrozole in subjects with liver cirrhosis were within the range of concentrations observed in healthy subjects in other studies. The plasma concentrations of anastrozole, which were measured in patients with hepatic impairment as part of long-term efficacy studies, were within the range of anastrozole plasma concentrations observed in patients without hepatic impairment.

In subjects with severe renal impairment (GFR <30 mL/min), the apparent clearance (CL/F) of anastrozole in Study 1033IL/0018 was unchanged after oral administration. This is consistent with the fact that anastrozole is mainly eliminated by metabolism. The plasma concentrations of anastrozole, which were measured in patients with renal impairment as part of long-term efficacy studies, were within the range of anastrozole plasma concentrations observed in patients without renal impairment. In patients with severe renal impairment, anastrozole should be used with caution (see section 4.2 and 4.4).

Paediatric population

In boys with pubertal gynaecomastia (10-17 years), anastrozole was rapidly absorbed, was largely systemically available and was eliminated slowly with a half-life of about 2 days. Anastrozole clearance in girls (3-10 years) was lower than in the older boys and exposure was higher. Anastrozole was also highly systemically available in girls and was eliminated slowly.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential or toxicity to reproduction in the indicated population.

Acute toxicity
In animal studies, toxicity was observed only at high dosages. In acute toxicity studies on rodents, the mean lethal anastrozole dose was more than 100 mg/kg/day for oral administration and more than 50 mg/kg/day for intraperitoneal administration. In an acute toxicity study on dogs, the mean lethal dose for oral administration was more than 45 mg/kg/day.

Chronic toxicity
In animal studies, toxicity was observed only at high dosages.
Repeated-dose toxicity studies have been performed in rats and dogs. Within the framework of toxicity studies, no no-effect level (dose without effect) was determined for anastrozole, but the effects observed at low (1 mg/kg/day) and medium doses (3 mg/kg/day in dogs and 5 mg/kg/day in rats) were attributable either to the pharmacological or enzyme-inducing properties of anastrozole and were not accompanied by significant toxic or degenerative changes.

Mutagenicity
Genotoxicity studies show that anastrozole has no mutagenic or clastogenic potential.

Toxicity to reproduction
In a fertility study, newly weaned male rats received doses of 50 or 400 mg/L anastrozole orally over 10 weeks via their drinking water. Mean plasma concentrations were determined to be 44.4 (± 14.7) ng/mL and 165 (± 90) ng/mL, respectively. Mating behaviour was adversely affected in both dosage groups, while a reduction in fertility became apparent only at the 400 mg/L dosage level. The reduction was transient, as all mating and fertility parameters were similar to the values in the control group after a 9-week treatment-free recovery period.

Oral administration of anastrozole to female rats led to a high incidence of infertility at a dosage of 1 mg/kg/day and increased pre-implantation loss at a dose of 0.02 mg/kg/day. These effects occurred at clinically relevant doses. An effect on humans cannot be excluded. These effects are related to the pharmacology of the active substance and were completely reversible after a 5-week active substance withdrawal phase.

Oral administration of anastrozole at dosages up to 1.0 mg/kg/day in pregnant rats and up to 0.2 mg/kg/day in pregnant rabbits had no teratogenic effect. The effects observed (placental enlargement in rats and termination of pregnancy in rabbits) were associated with the pharmacological effect of the substance.

The survival rate of rat pups administered anastrozole at doses of 0.02 mg/kg/day and above (from day 17 of gestation to day 22 *post partum*) was reduced. This effect is associated with the pharmacological effect of the substance on parturition. No adverse effects on the behaviour or reproductive performance of first-generation offspring were observed which could be attributed to the treatment of the dam with anastrozole.

Carcinogenicity
In a 2-year oncogenicity study in rats, only the administration of high doses (25 mg/kg/day) led to increased occurrence of liver tumours and uterine stromal polyps in female animals and thyroid adenomas in male animals. These changes occurred at a dose equivalent to 100-fold the therapeutic

doses in humans and are not considered clinically relevant for the treatment of patients with anastrozole.

A 2-year oncogenicity study in mice led to the formation of benign ovarian tumours and disturbance in the incidence of lymphoreticular neoplasms (fewer histiocytic sarcomas in female animals and more fatalities due to lymphomas). In mice, these changes are regarded as species-specific effects of aromatase inhibition and as clinically irrelevant for the treatment of patients with anastrozole.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Povidone (K30)
Sodium starch glycolate (type A)
Magnesium stearate [vegetable]

Film coating:
Hypromellose
Titanium dioxide
Macrogol 400

6.2 Incompatibilities

None

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store below 30 °C.

6.5 Nature and contents of container

PVC/PVDC/AL-blisters
Pack sizes: 30 film-coated 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 AUTHORISATION HOLDER

Denk Pharma GmbH & Co. KG
Prinzregentenstr. 79
81675 Munich
Germany

8. MARKETING AUTHORISATION NUMBER IN GERMANY

75126.00.00

9. DATE OF FIRST AUTHORISATION IN GERMANY

07/05/2010

10. DATE OF REVISION OF THE TEXT

12/2016

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.