# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Agerdex 1 mg film-coated tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1 mg anastrozole.

Excipients with known effect:
Each film-coated tablet contains 93 mg lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablet.
White film-coated round biconvex tablets, debossed with "ANA" and "1" on one side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Agerdex 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 who have received 2 to 3 years of adjuvant tamoxifen.

### 4.2 Posology and method of administration

Posology
The recommended dose of Agerdex for adults including the elderly is one 1 mg tablet once a day.

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

*Special populations*
*Paediatric population*
Agerdex is not recommended for use in children and adolescents due to insufficient data on safety and efficacy (see sections 4.4 and 5.1).

*Renal impairment*
No dose change is recommended in patients with mild or moderate renal impairment. In patients with severe renal impairment, administration of Agerdex should be performed with caution (see section 4.4 and 5.2).

*Hepatic impairment* No dose change is recommended in patients with mild hepatic disease. Caution is advised in patients with moderate to severe hepatic impairment (see section 4.4).

Method of administration
Agerdex should be taken orally.

### 4.3 Contraindications

Agerdex is contraindicated in:

- Pregnant or breast-feeding 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 should not be used in premenopausal women. The menopause should be defined biochemically (luteinising-hormone [LH], follicle stimulating hormone [FSH], and/or oestradiol levels) in any patient where there is doubt about menopausal status. There are no data to support the use of anastrozole with LHRH analogues.
Co-administration of tamoxifen or oestrogen-containing therapies with Agerdex should be avoided as this may diminish its pharmacological action (see section 4.5 and 5.1).

Effect on bone mineral density
As Anastrozole lowers circulating oestrogen levels it may cause a reduction in bone mineral density with a possible consequent increased risk of fracture (see section 4.8).
Women with osteoporosis or at risk of osteoporosis, should have their bone mineral density formally assessed at the commencement of treatment and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored. The use of specific treatments, e.g., bisphosphonates, may stop further bone mineral loss caused by Agerdex in postmenopausal women and could be considered (see section 4.8).

Hepatic impairment
Anastrozole has not been investigated in breast cancer patients with moderate or severe hepatic impairment. Exposure to anastrozole can be increased in subjects with hepatic impairment (see section 5.2); administration of anastrozole in patients with moderate and severe hepatic impairment should be performed with caution (see section 4.2). Treatment should be based on a benefit-risk evaluation for the individual patient.

Renal impairment
Anastrozole has not been investigated in breast cancer patients with severe renal impairment. Exposure to anastrozole is not increased in subjects with severe renal impairment (GRF<30ml/min, see section 5.2); in patients with severe renal impairment, administration of Agerdex should be performed with caution (see section 4.2).

Paediatric population
Anastrozole is not recommended for use in children and adolescents as safety and efficacy have not been established in this group of patients (see section 5.1).
Agerdex should not be used in boys with growth hormone deficiency in addition to growth hormone treatment. In the pivotal clinical trial, efficacy was not demonstrated and safety was not established (see section 5.1). Since anastrozole reduces estradiol levels, Agerdex must not be used in girls with growth hormone deficiency in addition to growth hormone treatment.
Long-term safety data in children and adolescents are not available.

Excipients with known effect
*Lactose*
This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

*Sodium*
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

**4.5 Interaction with other medicinal products and other forms of interaction**

Anastrozole inhibits CYPs 1A2, 2C8/9 and 3A4 in vitro. Clinical studies with antipyrine and warfarin showed that anastrozole at a 1 mg dose did not significantly inhibit the metabolism of antipyrine and R– and S-warfarin indicating the co-administration of Agerdex with other medicinal products is unlikely to result in clinically significant medicinal product interactions mediated by CYP enzymes.

The enzymes mediating metabolism of anastrozole have not been identified. Cimetidine, a weak, unspecific inhibitor of CYP enzymes, did not affect the plasma concentrations of anastrozole. The effect of potent CYP inhibitors is unknown.

A review of the clinical trial safety database did not reveal evidence of clinically significant interaction in patients treated with anastrozole who also received other commonly prescribed drugs. There were no clinically significant interactions with bisphosphonates (see section 5.1).

Co-administration of tamoxifen or oestrogen-containing therapies with Agerdex should be avoided as this may diminish its pharmacological action (see section 4.4 and 5.1).

**4.6 Fertility, pregnancy and lactation**

Pregnancy
There are no data from the use of anastrozole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Anastrozole is contraindicated during pregnancy (see section 4.3).

Breast-feeding
There are no data on the use of anastrozole during lactation. Anastrozole is contraindicated during breast-feeding (see section 4.3).

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**

Anastrozole has no or negligible influence on the ability to drive and use machines. However, asthenia and somnolence have been reported with the use of anastrozole and caution should be observed when driving or operating machinery while such symptoms persist.

**4.8 Undesirable effects**

The following table presents adverse reactions from clinical trials, post-marketing studies or spontaneous reports. Unless specified, the frequency categories were calculated from the number of adverse events reported in a large phase III study conducted in 9,366 postmenopausal women with operable breast cancer given adjuvant treatment for five years (the Anastrozole, Tamoxifen, Alone or in Combination [ATAC] study).

Adverse reactions listed below are classified according to frequency and System Organ Class (SOC). Frequency groupings 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) and not known (cannot be estimated from the available data). The most frequently reported adverse reactions were headache, hot flushes, nausea, rash, arthralgia, joint stiffness, arthritis, and asthenia.

**Table 1 Adverse reactions by System Organ Class and frequency**

| System Organ Class | Frequency | Adverse reaction |
|---|---|---|
| Metabolism and nutrition disorders | Common | Anorexia<br>Hypercholesterolaemia |
| | Uncommon | Hypercalcaemia (with or without an increase in parathyroid hormone) |
| Psychiatric disorders | Very common | Depression |
| Nervous system disorders | Very common | Headache |
| | Common | Somnolence<br>Carpal Tunnel Syndrome*<br>Sensory disturbances (including paraesthesia, taste loss and taste perversion) |
| | Not known | Memory impairment |
| Eye disorders | Not known | Dry eye |
| Vascular disorders | Very common | Hot flushes |
| Gastrointestinal disorders | Very common | Nausea |
| | Common | Diarrhoea<br>Vomiting |

| | | |
|---|---|---|
| Hepatobiliary disorders | Common | Increases in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase |
| | Uncommon | Increases in gamma-GT and bilirubin<br>Hepatitis |
| Skin and subcutaneous tissue disorders | Very common | Rash |
| | Common | Hair thinning (alopecia)<br>Allergic reactions |
| | Uncommon | Urticaria |
| | Rare | Erythema multiforme<br>Anaphylactoid reaction<br>Cutaneous vasculitis (including some reports of Henoch-Schönlein purpura)** |
| | Very rare | Stevens-Johnson Syndrome<br>Angioedema |
| | Not known | Lichenoid eruption |
| Musculoskeletal and connective tissue disorders | Very common | Arthralgia/joint stiffness<br>Arthritis<br>Osteoporosis |
| | Common | Bone pain<br>Myalgia |
| | Uncommon | Trigger finger |
| | Not known | Tendonitis<br>Tendon rupture |
| Reproductive system and breast disorders | Common | Vaginal dryness<br>Vaginal bleeding*** |
| General disorders and administration site conditions | Very common | Asthenia |

*Events of Carpal Tunnel Syndrome have been reported in patients receiving anastrozole treatment in clinical trials in greater numbers than those receiving treatment with tamoxifen. However, the majority of these events occurred in patients with identifiable risk factors for the development of the condition.
**Since cutaneous vasculitis and Henoch-Schönlein purpura was not observed in ATAC, 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 reported commonly, mainly in patients with advanced breast cancer during the first few weeks after changing from existing hormonal therapy to treatment with anastrozole. If bleeding persists, further evaluation should be considered.

The table below presents the frequency of pre-specified adverse events in the ATAC study after a median follow-up of 68 months, irrespective of causality, reported in patients receiving trial therapy and up to 14 days after cessation of trial therapy.

**Table 2 ATAC study pre-specified adverse events**

| **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 disturbances | 597 (19.3%) | 554 (17.9%) |
| Fatigue/asthenia | 575 (18.6%) | 544 (17.6%) |
| Nausea and vomiting | 393 (12.7%) | 384 (12.4%) |
| Fractures | 315 (10.2%) | 209 (6.8%) |
| Fractures of the spine, hip or wrist/Colles | 133 (4.3%) | 91 (2.9%) |
| Wrist/Colles fractures | 67 (2.2%) | 50 (1.6%) |
| Spine fractures | 43 (1.4%) | 22 (0.7%) |
| Hip fractures | 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 infarct | 37 (1.2%) | 34 (1.1%) |
| Coronary artery disorder | 25 (0.8%) | 23 (0.7%) |
| Myocardial ischaemia | 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 PE (pulmonary embolism) | 48 (1.6%) | 74 (2.4%) |
| Ischaemic cerebrovascular events | 62 (2.0%) | 88 (2.8%) |
| Endometrial cancer | 4 (0.2%) | 13 (0.6%) |

Fracture rates of 22 per 1000 patient-years and 15 per 1000 patient-years were observed for the anastrozole and tamoxifen groups, respectively, after a median follow-up of 68 months. The observed fracture rate for anastrozole is similar to 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 fracture and osteoporosis seen in ATAC in patients on anastrozole treatment reflect 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 HPRA Pharmacovigilance. Website: www.hpra.ie.

**4.9 Overdose**

There is limited clinical experience of accidental overdose. In animal studies, anastrozole demonstrated low acute toxicity. Clinical trials have been conducted with various dosages of anastrozole, up to 60 mg in a single dose given to healthy male volunteers, and up to 10 mg daily given to postmenopausal women with advanced breast cancer; these dosages were well tolerated. A single dose of anastrozole that results in life-threatening symptoms has not been established.
There is no specific antidote to overdose and treatment must be symptomatic.
In the management of an overdose, consideration should be given to the possibility that multiple agents may have been taken. Vomiting may be induced if the patient is alert.
Dialysis may be helpful because anastrozole is not highly protein-bound.
General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Hormone Antagonists and Related Agents Aromatase inhibitors

ATC Code: L02B G03

Mechanism of action and pharmacodynamic effects
Anastrozole is a potent and highly selective non-steroidal aromatase inhibitor. In postmenopausal women, oestradiol is produced primarily by the conversion of androstenedione to oestrone through the aromatase enzyme complex in peripheral tissues. Oestrone is subsequently converted to estradiol. Reducing circulating oestradiol levels has been shown to produce a beneficial effect in women with breast cancer.

In postmenopausal women, a daily dose of 1 mg of anastrozole produced oestradiol suppression of greater than 80% using a highly sensitive assay.

Anastrozole does not possess any progestogenic, androgenic or oestrogenic activity.

Daily doses of anastrozole up to 10 mg do not have any effect on cortisol or aldosterone secretion, measured before or after standard adrenocorticotrophic hormone (ACTH) challenge testing. Corticoid supplements are therefore not needed.

Clinical efficacy and safety

*Advanced breast cancer*
*First-line therapy in postmenopausal women with advanced breast cancer*
Two double-blind, controlled clinical studies of similar design (Study 1033IL/0030 and Study 1033IL/0027) were conducted to assess the efficacy of anastrozole compared with tamoxifen as first-line therapy for hormone receptor-positive or hormone receptor-unknown locally advanced or metastatic breast cancer in postmenopausal women. A total of 1,021 patients were

randomised to receive 1 mg of anastrozole once daily or 20 mg of tamoxifen once daily. The primary endpoints for both trials were time to tumour progression, objective tumour response rate, and safety.

For the primary endpoints, Study 1033IL/0030 showed that anastrozole had a statistically significant advantage over tamoxifen for time to tumour progression (Hazard ratio (HR) 1.42, 95% Confidence Interval (CI) [1.11, 1.82], Median time to progression 11.1 and 5.6 months for anastrozole and tamoxifen respectively, p=0.006); objective tumour response rates were similar for anastrozole and tamoxifen. Study 1033IL/0027 showed that anastrozole and tamoxifen had similar objective tumour response rates and time to tumour progression. Results from the secondary endpoints were supportive of the results of the primary efficacy endpoints. There were too few deaths occurring across treatment groups of both trials to draw conclusions on overall survival differences.

*Second-line therapy in postmenopausal women with advanced breast cancer*
Anastrozole was studied in two controlled clinical trials (Study 0004 and Study 0005) in postmenopausal women with advanced breast cancer who had disease progression following tamoxifen therapy 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 of anastrozole or megestrol acetate 40 mg four times a day. Time to progression and objective response rates were the primary efficacy variables. The rate of prolonged (more than 24 weeks) stable disease, the rate of progression, and survival were also calculated. In both studies there were no significant differences between treatment arms with respect to any of the efficacy parameters.

*Adjuvant treatment of early invasive breast cancer for hormone receptor-positive patients*
In a large phase III study conducted in 9366 postmenopausal women with operable breast cancer treated for 5 years, anastrozole was shown to be statistically superior to tamoxifen in disease free survival. A greater magnitude of benefit was observed for disease-free survival in favour of anastrozole versus tamoxifen for the prospectively defined hormone receptor positive population.

**Table 3 ATAC endpoint summary: 5-year treatment completion analysis**

| **ATAC endpoint summary: 5- year treatment completion analysis** | | | | |
|---|---|---|---|---|
| **Efficacy endpoints** | **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 | |
| 2-sided 95% CI | 0.78 to 0.97 | | 0.73 to 0.94 | |
| p-value | 0.0127 | | 0.0049 | |
| **Distant disease-free survival**[b] | 500 (16.0) | 530 (17.0) | 370 (14.1) | 394 (15.2) |
| Hazard ratio | 0.94 | | 0.93 | |
| 2-sided 95% CI | 0.83 to 1.06 | | 0.80 to 1.07 | |
| p-value | 0.2850 | | 0.2838 | |
| **Time to recurrence**[c] | 402 (12.9) | 498 (16.0) | 282 (10.8) | 370 (14.2) |
| Hazard ratio | 0.79 | | 0.74 | |
| 2-sided 95% CI | 0.70 to 0.90 | | 0.64 to 0.87 | |
| p-value | 0.0005 | | 0.0002 | |
| **Time to distant recurrence**[d] | 324 (10.4) | 375 (12.0) | 226 (8.6) | 265 (10.2) |
| Hazard ratio | 0.86 | | 0.84 | |
| 2-sided 95% CI | 0.74 to 0.99 | | 0.70 to 1.00 | |
| p-value | 0.0427 | | 0.0559 | |
| **Contralateral breast primary** | 35 (1.1) | 59 (1.9) | 26 (1.0) | 54 (2.1) |
| Odds ratio | 0.59 | | 0.47 | |
| 2-sided 95% CI | 0.39 to 0.89 | | 0.30 to 0.76 | |
| p-value | 0.0131 | | 0.0018 | |
| **Overall survival**[e] | 411 (13.2) | 420 (13.5) | 296 (11.3) | 301 (11.6) |
| Hazard ratio | 0.97 | | 0.97 | |
| 2-sided 95% CI | 0.85 to 1.12 | | 0.83 to 1.14 | |
| p-value | 0.7142 | | 0.7339 | |

[a] Disease-free survival includes all recurrence events and is defined as the first occurrence of loco-regional recurrence, contralateral new breast cancer, distant recurrence or death (for any reason).
[b] Distant disease-free survival is defined as the first occurrence of distant recurrence or death (for any reason).
[c] Time to recurrence is defined as the first occurrence of loco-regional recurrence, contralateral new breast cancer, distant recurrence or death due to breast cancer.
[d] Time to distant recurrence is defined as the first occurrence of distant recurrence or death due to breast cancer.
[e] Number (%) of patients who had died.

The combination of anastrozole and tamoxifen did not demonstrate any efficacy benefits in comparison with tamoxifen in all patients as well as in the hormone receptor-positive population. This treatment arm was discontinued from the study.
With an updated follow-up at a median of 10 years, long term comparison of the treatment effects of anastrozole relative to tamoxifen were shown to be consistent with previous analyses.

Adjuvant treatment of early breast cancer for patients being treated with adjuvant tamoxifen
In a phase III trial (Austrian Breast and Colorectal Cancer Study Group [ABCSG 8])conducted in 2579 postmenopausal women with hormone receptor positive early breast cancer who had received surgery with or without radiotherapy and no chemotherapy, switching to anastrozole after 2 years adjuvant treatment with tamoxifen was statistically superior in disease-free survival when compared to remaining on tamoxifen, after a median follow-up of 24 months.

**Table 4 ABCSG 8 trial endpoint and results summary without radiotherapy and no chemotherapy (see below)**

| **Efficacy endpoints** | **Number of events (frequency)** | |
|---|---|---|
| | **anastrozole (n=1297)** | **tamoxifen (n=1282)** |
| **Disease-free survival** | 65 (5.0) | 93 (7.3) |
| Hazard ratio | 0.67 | |
| 2-sided 95% CI | 0.49 to 0.92 | |
| p-value | 0.014 | |
| **Time to any recurrence** | 36 (2.8) | 66 (5.1) |
| Hazard ratio | 0.53 | |
| 2-sided 95% CI | 0.35 to 0.79 | |
| p-value | 0.002 | |
| **Time to distant recurrence** | 22 (1.7) | 41 (3.2) |
| Hazard ratio | 0.52 | |
| 2-sided 95% CI | 0.31 to 0.88 | |
| p-value | 0.015 | |
| **New contralateral breast cancer** | 7 (0.5) | 15 (1.2) |
| Odds ratio | 0.46 | |
| 2-sided 95% CI | 0.19 to 1.13 | |
| p-value | 0.090 | |
| **Overall survival** | 43(3.3) | 45 (3.5) |
| Hazard ratio | 0.96 | |
| 2-sided 95% CI | 0.63 to 1.46 | |
| p-value | 0.840 | |

Two further similar trials (GABG/ARNO 95 and ITA), in one of which patients had received surgery and chemotherapy, as well as a combined analysis of ABCSG 8 and GABG/ARNO 95, supported these results.

The anastrozole safety profile in these 3 studies was consistent with the known safety profile established in postmenopausal women with hormone receptor positive early breast cancer.

*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 anastrozole 1 mg/day were stratified to low, moderate and high risk groups according to their existing risk of fragility fracture. The primary efficacy parameter was the analysis of lumbar spine bone mass density using DEXA scanning. All patients received treatment with vitamin D and calcium. Patients in the low risk group received anastrozole alone (N=42), those in the moderate group were randomised to anastrozole plus risedronate 35 mg once a week (N=77) or anastrozole plus placebo (N=77) and those in the high risk group received anastrozole plus risedronate 35 mg once a week (N=38). The primary endpoint was change from baseline in lumbar spine bone mass density at 12 months.

The 12-month main analysis has shown that patients already at moderate to high risk of fragility fracture showed no decrease in their bone mass density (assessed by lumbar spine bone mineral density using DEXA scanning) when managed by using anastrozole 1 mg/day in combination with risedronate 35 mg once a week. In addition, a decrease in BMD which was not statistically significant was seen in the low risk group treated with anastrozole 1 mg/day alone. These findings were mirrored in the secondary efficacy variable of change from baseline in total hip BMD at 12 months.

This study provides evidence that the use of bisphosphonates could be considered in the management of possible bone mineral loss in postmenopausal women with early breast cancer scheduled to be treated with anastrozole.

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

The European Medicines Agency has waived the obligation to submit the results of studies with anastrozole in one or several 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, multi-centre study evaluated 52 pubertal boys (aged 11 to 16 years inclusive) with GHD treated for 12 to 36 months with anastrozole 1 mg/day or placebo in combination with growth hormone. Only 14 subjects on anastrozole completed 36 months.

No statistically significant difference from placebo was observed for the growth related parameters of predicted adult height, height, height SDS (standard deviation score), and height velocity. Final height data were not available. While the number of children treated was too limited to draw any reliable conclusions on safety, there was an increased fracture rate and a trend towards reduced bone mineral density in the anastrozole arm compared to placebo.

*Testotoxicosis*
An open-label, non-comparative, multi-centre study evaluated 14 male patients (aged 2 to 9 years) with familial male-limited precocious puberty, also known as testotoxicosis, treated with combination of anastrozole and bicalutamide. The primary objective was to assess the efficacy and safety of this combination regimen over 12 months. Thirteen out of the 14 patients enrolled completed 12 months of combination treatment (one patient was lost to follow-up). There was no significant difference in growth rate after 12 months of treatment, relative to the growth rate during the 6 months prior to entering the study.

*Gynaecomastia studies*
Trial 0006 was a randomised, double-blind, multi-centre study of 82 pubertal boys (aged 11-18 years inclusive) with gynaecomastia of greater than 12 months duration treated with anastrozole 1 mg/day or placebo daily for up to 6 months. No significant difference in the number of patients who had a 50% or greater reduction in total breast volume after 6 months of treatment was observed between the anastrozole 1 mg treated group and the placebo group.

Trial 0001 was an open-label, multiple-dose pharmacokinetic study of anastrozole 1 mg/day in 36 pubertal boys with gynaecomastia of less than 12 months' duration. The secondary objectives were to evaluate the proportion of patients with reductions from baseline in the calculated volume of gynaecomastia of both breasts combined of at least 50% between day 1 and after 6 months of study treatment, and patient tolerability and safety. A decrease in 50% or more of total breast volume was seen in 56% (20/36) of the boys after 6 months.

*McCune-Albright Syndrome study*
Trial 0046 was an international, multi-centre, open-label exploratory trial of 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 1 mg/day in patients with MAS. The efficacy of study treatment was based on the proportion of patients fulfilling defined criteria relating to vaginal bleeding, bone age, and growth velocity.

No statistically significant change in the frequency of vaginal bleeding days on treatment was observed. There were no clinically significant changes in Tanner staging, mean ovarian volume, or mean uterine volume. No statistically significant change in the rate of increase in bone age on treatment compared to the rate during baseline was observed. Growth rate (in

cm/year) was significantly reduced ($p<0.05$) from pre-treatment through month 0 to month 12, and from pre-treatment to the second 6 months (month 7 to month 12).

**5.2 Pharmacokinetic properties**

Absorption
Absorption of anastrozole is rapid and maximum plasma concentrations typically occur within two hours of dosing (under fasted conditions). Food slightly decreases the rate but not the extent of absorption. The small change in the rate of absorption is not expected to result in a clinically significant effect on steady-state plasma concentrations during once daily dosing of Anastrozole tablets. Approximately 90 to 95% of plasma anastrozole steady-state concentrations are attained after 7 daily doses, and accumulation is 3- to 4-fold. There is no evidence of time or dose-dependency of anastrozole pharmacokinetic parameters.

Anastrozole pharmacokinetics are independent of age in postmenopausal women.

Distribution
Anastrozole is only 40% bound to plasma proteins.

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

Renal or hepatic impairment
The apparent clearance (CL/F) of anastrozole, following oral administration, was approximately 30% lower in volunteers with stable hepatic cirrhosis than in matched controls (Study 1033IL/0014). However, plasma anastrozole concentrations in the volunteers with hepatic cirrhosis were within the range of concentrations seen in normal subjects in other trials. Plasma anastrozole concentrations observed during long-term efficacy trials in patients with hepatic impairment were within the range of plasma anastrozole concentrations seen in patients without hepatic impairment.

The apparent clearance (CL/F) of anastrozole, following oral administration, was not altered in volunteers with severe renal impairment (GFR <30ml/min) in Study 1033IL/0018, consistent with the fact that anastrozole is eliminated primarily by metabolism. Plasma anastrozole concentrations observed during long-term efficacy trials in patients with renal impairment were within the range of plasma anastrozole concentrations seen in patients without renal impairment. In patients with severe renal impairment, administration of anastrozole should be performed with caution (see section 4.2 and 4.4).

Paediatric population
In boys with pubertal gynaecomastia (10-17 years), anastrozole was rapidly absorbed, was widely distributed, and was eliminated slowly with a half-life of approximately 2 days. Clearance of anastrozole was lower in girls (3-10 years) than in the older boys and exposure higher. Anastrozole in girls was widely distributed and slowly eliminated.

**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, toxicity to reproduction for the indicated population.

Acute toxicity
In animal studies toxicity was only seen at high doses. In acute toxicity studies in rodents, the median lethal dose of anastrozole was greater than 100 mg/kg/day by the oral route and greater than 50 mg/kg/day by the intraperitoneal route. In an oral acute toxicity study in the dog, the median lethal dose was greater than 45 mg/kg/day.

Chronic toxicity
In animal studies adverse effects were only seen at high doses. Multiple dose toxicity studies utilised rats and dogs. No no-effect levels were established for anastrozole in the toxicity studies, but those effects that were observed at the low doses (1 mg/kg/day) and mid doses (dog 3 mg/kg/day; rat 5 mg/kg/day) were related to either the pharmacological or enzyme inducing properties of anastrozole and were unaccompanied by significant toxic or degenerative changes.

Mutagenicity
Genetic toxicology studies with anastrozole show that it is not a mutagen or a clastogen.

Reproductive toxicology
In a fertility study weanling male rats were dosed orally with 50 or 400 mg/l anastrozole via their drinking water for 10 weeks. Measured mean plasma concentrations were 44.4 (± 14.7) ng/ml and 165 (±90) ng/ml respectively. Mating indices were adversely affected in both dose groups, whilst a reduction in fertility was evident only at the 400 mg/l dose level. The reduction was transient as all mating and fertility parameters were similar to control group values following a 9-week treatment-free recovery period.

Oral administration of anastrozole to female rats produced a high incidence of infertility at 1 mg/kg/day and increased pre-implantation loss at 0.02 mg/kg/day. These effects occurred at clinically relevant doses. An effect in man cannot be excluded. These effects were related to the pharmacology of the compound and were completely reversed after a 5-week compound withdrawal period.

Oral administration of anastrozole to pregnant rats and rabbits caused no teratogenic effects at doses up to 1.0 and 0.2 mg/kg/day respectively. Those effects that were seen (placental enlargement in rats and pregnancy failure in rabbits) were related to the pharmacology of the compound.

The survival of litters born to rats given anastrozole at 0.02 mg/kg/day and above (from Day 17 of pregnancy to Day 22 post-partum) was compromised. These effects were related to the pharmacological effects of the compound on parturition. There were no adverse effects on behaviour or reproductive performance of the first generation offspring attributable to maternal treatment with anastrozole.

Carcinogenicity
A two-year rat oncogenicity study resulted in an increase in incidence of hepatic neoplasms and uterine stromal polyps in females and thyroid adenomas in males at the high dose (25 mg/kg/day) only. These changes occurred at a dose which represents 100-fold greater exposure than occurs at human therapeutic doses, and are considered not to be clinically relevant to the treatment of patients with anastrozole.

A two-year mouse oncogenicity study resulted in the induction of benign ovarian tumours and a disturbance in the incidence of lymphoreticular neoplasms (fewer histiocytic sarcomas in females and more deaths as a result of lymphomas). These changes are considered to be mouse-specific effects of aromatase inhibition and not clinically relevant to the treatment of patients with anastrozole.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core
Lactose monohydrate
Sodium starch glycolate (type A)
Povidone (K31) (E1201)
Magnesium stearate (E572)

Film-coating
Macrogol 400
Hypromellose (E464)
Titanium dioxide (E171)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

48 months.

**6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

**6.5 Nature and contents of container**

Cardboard boxes containing PVC/PE/PVDC/Aluminium blisters of 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100 or 300 tablets and hospital blisters (PVC/PE/PVDC/ Aluminium) with 28, 50, 84, 98, 300 or 500 tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Viatris Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
Dublin
Ireland

**8 MARKETING AUTHORISATION NUMBER**

PA23266/075/001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 9th November 2007

Date of last renewal: 31st October 2009

**10 DATE OF REVISION OF THE TEXT**

January 2026