SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Amidex 1 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 1 mg of anastrozole.

Excipients: Lactose monohydrate 92.75 mg
For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, round, biconvex tablets with imprint A1 on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of advanced breast cancer in postmenopausal women. Efficacy has not been demonstrated in oestrogen receptor negative patients unless they had a previous positive clinical response to tamoxifen.

4.2 Posology and method of administration

Adults including the elderly
One film-coated tablet (1 mg) to be taken orally once a day.

Children and adolescents
Anastrozole is not recommended for use in children.

Renal and hepatic impairment
No dose change is recommended in patients with mild or moderate renal impairment.
No dose change is recommended in patients with mild hepatic disease.

For early disease, the recommended duration of treatment should be 5 years.

4.3 Contraindications

Amidex is contraindicated in:
- premenopausal women
- pregnant or lactating women
- patients with severe renal impairment (creatinine clearance less than 20 ml/min)
- patients with moderate or severe hepatic disease
- patients with known hypersensitivity to anastrozole or to any of the excipients as referenced in section 6.1

Oestrogen-containing therapies should not be co-administered with anastrozole as they would negate its pharmacological action.

Concurrent tamoxifen therapy (see section 4.5).

4.4 Special warnings and precautions for use

Amidex is not recommended for use in children and adolescents as safety and efficacy have not been established in this group of patients.

The menopause should be defined biochemically in any patient where there is doubt about hormonal status.

There are no data to support the safe use of anastrozole in patients with moderate or severe hepatic impairment, or patients with severe impairment of renal function (creatinine clearance less than 20 ml/min).

Women with osteoporosis or at risk of osteoporosis, should have their bone mineral density formally assessed by bone densitometry e.g. DEXA scanning at the commencement of treatment and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored.

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

As anastrozole lowers circulating oestrogen levels it may cause a reduction in bone mineral density. Adequate data to show the effect of bisphosphonates on bone mineral density loss caused by anastrozole, or their utility when used prophylactically, are not currently available.

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

4.5 Interaction with other medicinal products and other forms of interaction

Anastrozole inhibited cytochrome P450 1A2, 2C8/9 and 3A4 *in vitro*, but a clinical interaction study with warfarin indicated that anastrozole at a 1 mg dose does not significantly inhibit the metabolism of substances that are metabolised via cytochrome P450.

No clinically significant interactions between anastrozole and bisphosphonates have been identified.

Tamoxifen should not be co-administered with anastrozole, as this may diminish its pharmacological action (see section 4.3).

4.6 Pregnancy and lactation

Amidex is contraindicated in pregnant and lactating women (see section 4.3).

Pregnancy
There are no data on the use of anastrozole in pregnant patients. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Anastrozole is contraindicated in pregnant women.

Lactation
It is unknown whether anastrozole is excreted in human milk. Anastrozole is contraindicated in lactating women.

4.7 Effects on ability to drive and use machines

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

Amidex is unlikely to impair the ability of patients to drive and operate machinery. 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

Rates of incidence:
very common (> 1/10)
common (≥ 1/100, < 1/10)
uncommon (≥ 1/1,000, < 1/100)
rare (≥ 1/10,000, < 1/1,000)
very rare (≤ 1/10,000), not known (cannot be estimated from the available data)

	very common	common	uncommon	very rare
Nervous system disorders		Headache, mainly mild or moderate in nature Carpal tunnel syndrome	Somnolence, mainly mild or moderate in nature	
Gastrointestinal disorders		Nausea, mainly mild or moderate in nature Diarrhoea, mainly mild or moderate in nature	Vomiting, mainly mild or moderate in nature	
Skin and subcutaneous tissue disorders		Hair thinning, mainly mild or moderate in nature Rash, mainly mild or moderate in nature		Erythema multiforme Stevens-Johnson syndrome Allergic reactions including angioedema, urticaria and anaphylaxis
Musculoskeletal, connective tissue and bone disorders		Joint pain/stiffness, mainly mild or moderate in nature		
Metabolism and nutrition disorders			Anorexia, mainly mild or moderate in nature Hypercholesterol-aemia, mainly mild or moderate in nature	
Vascular disorders	Hot flushes, mainly mild or moderate in nature			
General disorders and administration site conditions		Asthenia, mainly mild or moderate in nature		
Hepatobiliary disorders		Increases in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase	Elevated gamma-GT and bilirubin. Hepatitis	

	very common	common	uncommon	very rare
Reproductive system and breast disorders		Vaginal dryness, mainly mild or moderate in nature	Vaginal bleeding*, mainly mild or moderate in nature	

*Vaginal bleeding has been reported uncommonly, 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.

As anastrozole lowers circulating oestrogen levels, it may cause a reduction in bone mineral density placing some patients at a higher risk of fracture (see section 4.4).

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

Adverse event	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 fractures	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 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. 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.

The incidence of osteoporosis was 10.5% in patients treated with anastrozole and 7.3% in patients treated with tamoxifen.

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. Absorption can be lowered by gastric lavage followed by administration of activated charcoal or charcoal. 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: Enzyme inhibitors
ATC Code: L02B G03

Anastrozole is a potent and highly selective non-steroidal aromatase inhibitor. In postmenopausal women, estradiol is produced primarily from the conversion of androstenedione to estrone through the aromatase enzyme complex in peripheral tissues. Estrone is subsequently converted to estradiol. Reducing circulating estradiol levels has been shown to produce a beneficial effect in women with breast cancer. In postmenopausal women, anastrozole at a daily dose of 1 mg produced estradiol suppression of greater than 80% using a highly sensitive assay method.

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 ACTH challenge testing. Corticoid supplements are therefore not needed.

Primary adjuvant treatment of early breast cancer

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. Anastrozole was statistically superior to tamoxifen in time to recurrence. The difference was of even greater magnitude than in disease free survival for both the Intention To Treat (ITT) population and hormone receptor positive population. Anastrozole was statistically superior to tamoxifen in terms of time to distant recurrence. The incidence of contralateral breast cancer was statistically reduced for anastrozole compared to tamoxifen.

Following 5 years of therapy, anastrozole is at least as effective as tamoxifen in terms of overall survival. However, due to low death rates, additional follow-up is required to determine more precisely the long-term survival for anastrozole relative to tamoxifen. With 68 months median follow-up, patients in the ATAC study have not been followed up for sufficient time after 5 years of treatment, to enable a comparison of long-term post treatment effects of anastrozole relative to tamoxifen.

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.

As with all treatment decisions, women with breast cancer and their physician should assess the relative benefits and risks of the treatment.

When anastrozole and tamoxifen were co-administered, the efficacy and safety were similar to tamoxifen when given alone, irrespective of hormone receptor status. The exact mechanism of this is not yet clear. It is not believed to be due to a reduction in the degree of estradiol suppression produced by anastrozole.

Adjuvant treatment of early breast cancer for patients being treated with adjuvant tamoxifen

In a phase III trial (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.

Time to any recurrence, time to local or distant recurrence and time to distant recurrence confirmed a statistical advantage for anastrozole, consistent with the results of disease-free survival.

The incidence of contralateral breast cancer was very low in the two treatment arms with a numerical advantage for anastrozole. Overall survival was similar for the two treatment groups.

ABCSG 8 trial endpoint and results summary		
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 local or distant recurrence	29 (2.2)	51 (4.0)
Hazard ratio	0.55	
2-sided 95% CI	0.35 to 0.87	
p-value	0.011	
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.

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. There is no evidence of time or dose-dependency of anastrozole pharmacokinetic parameters.

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.

Metabolism
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.
The apparent oral clearance of anastrozole in volunteers with stable hepatic cirrhosis or renal impairment was in the range observed in healthy volunteers.

Age dependency of pharmacokinetics
Anastrozole pharmacokinetics are independent of age in postmenopausal women.

Pharmacokinetics in children and adolescents
Pharmacokinetics have not been studied in children and adolescents.

5.3 Preclinical safety data

In animal studies, toxicity related to the pharmacodynamic action was only seen at high doses.

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 was compromised. These effects were related to the pharmacological effects of the compound on parturition.

Genetic toxicology studies with anastrozole show that it is neither a mutagen nor a clastogen.

Carcinogenicity studies have been performed in rats and mice.
In rats, increases in the incidence of hepatic neoplasms and uterine stromal polyps in females and thyroid adenomas in males were observed at a dose which represents 100-fold greater exposure than occurs at human therapeutic doses. These changes are considered not to be clinically relevant.
In mice 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) were observed. These changes are considered to be mouse-specific effects of aromatase inhibition and not clinically relevant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Sodium starch glycolate (Type A)
Povidone K-25
Magnesium stearate

Film coating
Hypromellose
Macrogol 6000
Cottonseed oil, hydrogenated
Starch, pregelatinised modified (origin: maize)
Titanium dioxide E171

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and content of container

PVC/Aluminium blister.

Pack sizes: 28, 30, 50, 90, 98, 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel
Co. Tipperary

8. MARKETING AUTHORISATION NUMBER

PA 126/189/1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 24th July 2009

10. DATE OF (PARTIAL) REVISION OF THE TEXT

December 2009