SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Femara 2.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: letrozole.

Each film-coated tablet contains 2.5 mg letrozole.

Excipients of known effect: Each tablet contains 61.5mg of lactose (monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Dark yellow, round, slightly biconvex with bevelled edges. One side bears the imprint “FV”, the other “CG”.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.
- Extended adjuvant treatment of hormone dependent invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy for 5 years.
- First line treatment in postmenopausal women with hormone dependent advanced breast cancer.
- Advanced breast cancer after relapse or disease progression, in women with natural or artificially induced postmenopausal endocrine status, who have previously been treated with anti-oestrogens.
- Neo-adjuvant treatment of postmenopausal women with hormone receptor positive, HER-2 negative breast cancer where chemotherapy is not suitable and immediate surgery not indicated.

Efficacy has not been demonstrated in patients with hormone receptor negative breast cancer.

4.2 Posology and method of administration

Posology

Adult and elderly patients

The recommended dose of Femara is 2.5 mg once daily. No dose adjustment is required for elderly patients.

In patients with advanced or metastatic breast cancer, treatment with Femara should continue until tumour progression is evident.

In the adjuvant and extended adjuvant setting, treatment with Femara should continue for 5 years or until tumour relapse occurs, whichever is first.
In the adjuvant setting a sequential treatment schedule (letrozole 2 years followed by tamoxifen 3 years) could also be considered (see sections 4.4 and 5.1).
In the neoadjuvant setting, treatment with Femara could be continued for 4 to 8 months in order to establish optimal tumour reduction. If the response is not adequate, treatment with Femara should be discontinued and surgery scheduled and/or further treatment options discussed with the patient.

Paediatric population

Femara is not recommended for use in children and adolescents. The safety and efficacy of Femara in children and adolescents aged up to 17 years have not been established. Limited data are available and no recommendation on a posology can be made.

Renal impairment

No dosage adjustment of Femara is required for patients with renal insufficiency with creatinine clearance ≥10 ml/min. Insufficient data are available in cases of renal insufficiency with creatinine clearance lower than 10 ml/min (see sections 4.4 and 5.2).

Hepatic impairment

No dose adjustment of Femara is required for patients with mild to moderate hepatic insufficiency (Child-Pugh A or B). Insufficient data are available for patients with severe hepatic impairment. Patients with severe hepatic impairment (Child-Pugh C) require close supervision (see sections 4.4 and 5.2).

Method of administration

Femara should be taken orally and can be taken with or without food.

A missed dose should be taken as soon as the patient remembers. However, if it is almost time for the next dose (within 2 or 3 hours), the missed dose should be skipped, and the patient should go back to her regular dosage schedule. Doses should not be doubled because with daily doses over the 2.5 mg recommended dose, over-proportionality in systemic exposure was observed (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Premenopausal endocrine status
- Pregnancy (see section 4.6)
- Breast-feeding (see section 4.6)

4.4 Special warnings and precautions for use

Menopausal status

In patients whose menopausal status is unclear, luteinising hormone (LH), follicle-stimulating hormone (FSH) and/or oestradiol levels should be measured before initiating treatment with Femara. Only women of postmenopausal endocrine status should receive Femara.

Renal impairment

Femara has not been investigated in a sufficient number of patients with a creatinine clearance lower than 10 ml/min. The potential risk/benefit to such patients should be carefully considered before administration of Femara.

Hepatic impairment

In patients with severe hepatic impairment (Child-Pugh C), systemic exposure and terminal half-life were approximately doubled compared to healthy volunteers. Such patients should therefore be kept under close supervision (see section 5.2).

Bone effects

Femara is a potent oestrogen-lowering agent. Women with a history of osteoporosis and/or fractures, or who are at increased risk of osteoporosis, should have their bone mineral density formally assessed prior to the commencement of adjuvant and extended adjuvant treatment and monitored during and following treatment with letrozole. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored. In the adjuvant setting a sequential treatment schedule (letrozole 2 years followed by tamoxifen 3 years) could also be considered depending on the patient's safety profile (see sections 4.2, 4.8 and 5.1).

Tendonitis and tendon rupture

Tendonitis and tendon ruptures (rare) may occur. Close monitoring of the patients and appropriate

measures (e.g. immobilisation) must be initiated for the affected tendon (see section 4.8).

Other warnings

Co-administration of Femara with tamoxifen, other anti-oestrogens or oestrogen-containing therapies should be avoided as these substances may diminish the pharmacological action of letrozole (see section 4.5).

Femara contains lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Femara contains 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

Metabolism of letrozole is partly mediated via CYP2A6 and CYP3A4. Cimetidine, a weak, unspecific inhibitor of CYP450 enzymes, did not affect the plasma concentrations of letrozole. The effect of potent CYP450 inhibitors is unknown.

There is no clinical experience to date on the use of Femara in combination with oestrogens or other anticancer agents, other than tamoxifen. Tamoxifen, other anti-oestrogens or oestrogen-containing therapies may diminish the pharmacological action of letrozole. In addition, co-administration of tamoxifen with letrozole has been shown to substantially decrease plasma concentrations of letrozole. Co-administration of letrozole with tamoxifen, other anti-oestrogens or oestrogens should be avoided.

In vitro, letrozole inhibits the cytochrome P450 isoenzymes 2A6 and, moderately, 2C19, but the clinical relevance is unknown. Caution is therefore indicated when giving letrozole concomitantly with medicinal products whose elimination is mainly dependent on these isoenzymes and whose therapeutic index is narrow (e.g. phenytoin, clopidrogel).

4.6 Fertility, pregnancy and lactation

Women of perimenopausal status or child-bearing potential
Femara should only be used in women with a clearly established postmenopausal status (see section 4.4). As there are reports of women regaining ovarian function during treatment with Femara despite a clear postmenopausal status at start of therapy, the physician needs to discuss adequate contraception when necessary.

Pregnancy
Based on human experience in which there have been isolated cases of birth defects (labial fusion, ambiguous genitalia), Femara may cause congenital malformations when administered during pregnancy. Studies in animals have shown reproductive toxicity (see section 5.3).

Femara is contraindicated during pregnancy (see sections 4.3 and 5.3).

Breast-feeding
It is unknown whether letrozole/ metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.

Femara is contraindicated during breast-feeding (see section 4.3).

Fertility
The pharmacological action of letrozole is to reduce oestrogen production by aromatase inhibition. In premenopausal women, the inhibition of oestrogen synthesis leads to feedback increases in gonadotropin (LH, FSH) levels. Increased FSH levels in turn stimulate follicular growth, and can induce ovulation.

4.7 Effects on ability to drive and use machines

Femara has minor influence on the ability to drive and use machines. Since fatigue and dizziness have been observed with the use of Femara and somnolence has been reported uncommonly, caution is advised when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile
The frequencies of adverse reactions for Femara are mainly based on data collected from clinical studies.

Up to approximately one third of the patients treated with Femara in the metastatic setting and approximately 80% of the patients in the adjuvant setting as well as in the extended adjuvant setting experienced adverse reactions. The majority of the adverse reactions occurred during the first few weeks of treatment.

The most frequently reported adverse reactions in clinical studies were hot flushes, hypercholesterolaemia, arthralgia, fatigue, increased sweating and nausea.

Important additional adverse reactions that may occur with Femara are: skeletal events such as osteoporosis and/or bone fractures and cardiovascular events (including cerebrovascular and thromboembolic events). The frequency category for these adverse reactions is described in Table 1.

Tabulated list of adverse reactions
The frequencies of adverse reactions for Femara are mainly based on data collected from clinical studies.

The following adverse drug reactions, listed in Table 1, were reported from clinical studies and from post-marketing experience with Femara:

Table 1 Adverse reactions
Adverse reactions are ranked under headings of frequency, the most frequent first, using 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); not known (cannot be estimated from the available data).

Infections and infestations
Uncommon: Urinary tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)
Uncommon: Tumour pain[1]
Blood and lymphatic system disorders
Uncommon: Leukopenia
Immune system disorders
Not known: Anaphylactic reaction
Metabolism and nutrition disorders
Very common: Hypercholesterolaemia
Common: Decreased appetite, increased appetite

Psychiatric disorders
Common: Depression
Uncommon: Anxiety (including nervousness), irritability
Nervous system disorders
Common: Headache, dizziness
Uncommon: Somnolence, insomnia, memory impairment, dysaesthesia (including paraesthesia, hypoaesthesia), dysgeusia, cerebrovascular accident, carpal tunnel syndrome
Eye disorders
Uncommon Cataract, eye irritation, blurred vision
Cardiac disorders
Common: Palpitations[1]
Uncommon: Tachycardia, ischaemic cardiac events (including new or worsening angina, angina requiring surgery, myocardial infarction and myocardial ischaemia)
Vascular disorders
Very common: Hot flushes
Common: Hypertension
Uncommon: Thrombophlebitis (including superficial and deep vein thrombophlebitis)
Rare: Pulmonary embolism, arterial thrombosis, cerebral infarction
Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea, cough
Gastrointestinal disorders
Common: Nausea, dyspepsia[1], constipation, abdominal pain, diarrhoea, vomiting
Uncommon: Dry mouth, stomatitis[1]
Hepatobiliary disorders
Uncommon: Increased hepatic enzymes, hyperbilirubinaemia, jaundice
Not known: Hepatitis
Skin and subcutaneous tissue disorders
Very common: Hyperhidrosis
Common: Alopecia, rash (including erythematous, maculopapular, psoriaform, and vesicular rash), dry skin
Uncommon: Pruritus, urticaria
Not known: Angioedema, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders
Very common: Arthralgia
Common: Myalgia, bone pain[1], osteoporosis, bone fractures, arthritis
Uncommon: Tendonitis
Rare: Tendon rupture
Not known: Trigger finger
Renal and urinary disorders

Uncommon:	Pollakiuria
Reproductive system and breast disorders	
Common:	Vaginal haemorrhage
Uncommon:	Vaginal discharge, vulvovaginal dryness, breast pain
General disorders and administration site conditions	
Very common:	Fatigue (including asthenia, malaise)
Common:	Peripheral oedema, chest pain
Uncommon:	General oedema, mucosal dryness, thirst, pyrexia
Investigations	
Common:	Weight increased
Uncommon:	Weight decreased

[1] Adverse drug reactions reported only in the metastatic setting

Some adverse reactions have been reported with notably different frequencies in the adjuvant treatment setting. The following tables provide information on significant differences in Femara versus tamoxifen monotherapy and in the Femara-tamoxifen sequential treatment therapy:

Table 2 Adjuvant Femara monotherapy versus tamoxifen monotherapy – adverse events with significant differences

	Femara, incidence rate		**Tamoxifen, incidence rate**	
	N=2448		**N=2447**	
	During treatment (Median 5y)	**Any time after randomisation (Median 8y)**	**During treatment (Median 5y)**	**Any time after randomisation (Median 8y)**
Bone fracture	10.2%	14.7%	7.2%	11.4%
Osteoporosis	5.1%	5.1%	2.7%	2.7%
Thromboembolic events	2.1%	3.2%	3.6%	4.6%
Myocardial infarction	1.0%	1.7%	0.5%	1.1%
Endometrial hyperplasia / endometrial cancer	0.2%	0.4%	2.3%	2.9%

Note: "During treatment" includes 30 days after last dose. "Any time" includes follow-up period after completion or discontinuation of study treatment.
Differences were based on risk ratios and 95% confidence intervals.

Table 3 Sequential treatment versus Femara monotherapy – adverse events with significant differences

	Femara monotherapy	**Femara->tamoxifen**	**Tamoxifen->Femara**
	N=1535	**N=1527**	**N=1541**
	5 years	**2 yrs-> 3 yrs**	**2 yrs-> 3 yrs**
Bone fractures	10.0%	7.7%*	9.7%
Endometrial proliferative disorders	0.7%	3.4%**	1.7%**
Hypercholesterolaemia	52.5%	44.2%*	40.8%*
Hot flushes	37.6%	41.7%**	43.9%**
Vaginal bleeding	6.3%	9.6%**	12.7%**

* Significantly less than with Femara monotherapy
** Significantly more than with Femara monotherapy
Note: Reporting period is during treatment or within 30 days of stopping treatment

Description of selected adverse reactions

Cardiac adverse reactions
In the adjuvant setting, in addition to the data presented in Table 2, the following adverse events were reported for Femara and tamoxifen, respectively (at median treatment duration of 60 months plus 30 days): angina requiring surgery (1.0% vs. 1.0%); cardiac failure (1.1% vs. 0.6%); hypertension (5.6% vs. 5.7%); cerebrovascular accident/transient ischaemic attack (2.1% vs. 1.9%).

In the extended adjuvant setting for Femara (median duration of treatment 5 years) and placebo (median duration of treatment 3 years), respectively: angina requiring surgery (0.8% vs. 0.6%); new or worsening angina (1.4% vs. 1.0%); myocardial infarction (1.0% vs. 0.7%); thromboembolic event* (0.9% vs. 0.3%); stroke/transient ischaemic attack* (1.5% vs. 0.8%) were reported.

Events marked * were statistically significantly different in the two treatment arms.

Skeletal adverse reactions
For skeletal safety data from the adjuvant setting, please refer to Table 2.

In the extended adjuvant setting, significantly more patients treated with Femara experienced bone fractures or osteoporosis (bone fractures, 10.4% and osteoporosis, 12.2%) than patients in the placebo arm (5.8% and 6.4%, respectively). Median duration of treatment was 5 years for Femara, compared with 3 years for placebo.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Isolated cases of overdose with Femara have been reported.

No specific treatment for overdose is known; treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Endocrine therapy. Hormone antagonist and related agents: aromatase inhibitor, ATC code: L02BG04.

Mechanism of action
Letrozole is a non-steroidal aromatase inhibitor. It inhibits the aromatase enzyme by competitively binding to the haem of the aromatase cytochrome P450, resulting in a reduction of oestrogen biosynthesis in all tissues where present.

Pharmacodynamic effects

The elimination of oestrogen-mediated growth stimulation is a prerequisite for tumour response in cases where the growth of tumour tissue depends on the presence of oestrogens and endocrine therapy is used. In postmenopausal women, oestrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens - primarily androstenedione and testosterone - to oestrone and oestradiol. The suppression of oestrogen biosynthesis in peripheral tissues and the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme.

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Clinical efficacy and safety

In healthy postmenopausal women, single doses of 0.1 mg, 0.5 mg, and 2.5 mg letrozole suppress serum oestrone and oestradiol by 75%, 78% and 78% from baseline respectively. Maximum suppression is achieved in 48-78 hours.

In postmenopausal patients with advanced breast cancer, daily doses of 0.1 mg to 5 mg suppressed plasma concentration of oestradiol, oestrone, and oestrone sulphate by 75-95% from baseline in all patients treated. With doses of 0.5 mg and higher, many values of oestrone and oestrone sulphate were below the limit of detection in the assays, indicating that higher oestrogen suppression is achieved with these doses. Oestrogen suppression was maintained throughout treatment in all these patients.

Letrozole is highly specific in inhibiting aromatase activity. Impairment of adrenal steroidogenesis has not been observed. No clinically relevant changes were found in the plasma concentrations of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxyprogesterone, and ACTH or in plasma renin activity among postmenopausal patients treated with a daily dose of letrozole 0.1 to 5 mg. The ACTH stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 2.5 mg, and 5 mg did not indicate any attenuation of aldosterone or cortisol production. Thus, glucocorticoid and mineralocorticoid supplementation is not necessary.

No changes were noted in plasma concentrations of androgens (androstenedione and testosterone) among healthy postmenopausal women after 0.1 mg, 0.5 mg, and 2.5 mg single doses of letrozole or in plasma concentrations of androstenedione among postmenopausal patients treated with daily doses of 0.1 mg to 5 mg, indicating that the blockade of oestrogen biosynthesis does not lead to accumulation of androgenic precursors. Plasma levels of LH and FSH are not affected by letrozole in patients, nor is thyroid function as evaluated by TSH, T4, and T3 uptake test.

Adjuvant treatment

Study BIG 1-98

BIG 1-98 was a multicentre, double-blind study in which over 8,000 postmenopausal women with hormone receptor-positive early breast cancer were randomised to one of the following treatments: A. tamoxifen for 5 years; B. Femara for 5 years; C. tamoxifen for 2 years followed by Femara for 3 years; D. Femara for 2 years followed by tamoxifen for 3 years.

The primary endpoint was disease-free survival (DFS); secondary efficacy endpoints were time to distant metastasis (TDM), distant disease-free survival (DDFS), overall survival (OS), systemic disease-free survival (SDFS), invasive contralateral breast cancer and time to breast cancer recurrence.

Efficacy results at a median follow-up of 26 and 60 months

Data in Table 4 reflect the results of the Primary Core Analysis (PCA) based on data from the monotherapy arms (A and B) and from the two switching arms (C and D) at a median treatment

duration of 24 months and a median follow-up of 26 months and at a median treatment duration of 32 months and a median follow-up of 60 months.

The 5-year DFS rates were 84% for Femara and 81.4% for tamoxifen.

Table 4 Primary Core Analysis: Disease-free and overall survival, at a median follow-up of 26 months and at median follow-up of 60 months (ITT population)

	Primary Core Analysis Median follow-up 26 months			**Median follow-up 60 months**		
	Femara N=4003	**Tamoxifen N=4007**	**HR[1] (95% CI) *P***	**Femara N=4003**	**Tamoxifen N=4007**	**HR[1] (95% CI) *P***
Disease-free survival (primary) - events (protocol definition[2])	351	428	0.81 (0.70, 0.93) 0.003	585	664	0.86 (0.77, 0.96) 0.008
Overall survival (secondary) Number of deaths	166	192	0.86 (0.70, 1.06)	330	374	0.87 (0.75, 1.01)

HR = Hazard ratio; CI = Confidence interval

[1] Log rank test, stratified by randomisation option and use of chemotherapy (yes/no)

[2] DFS events: loco-regional recurrence, distant metastasis, invasive contralateral breast cancer, second (non-breast) primary malignancy, death from any cause without a prior cancer event.

Results at a median follow-up of 96 months (monotherapy arms only)

The Monotherapy Arms Analysis (MAA) long-term update of the efficacy of Femara monotherapy compared to tamoxifen monotherapy (median duration of adjuvant treatment: 5 years) is presented in Table 5.

Table 5 Monotherapy Arms Analysis: Disease-free and overall survival at a median follow-up of 96 months (ITT population)

	Femara N=2463	**Tamoxifen N=2459**	**Hazard Ratio[1] (95% CI)**	***P* Value**
Disease-free survival events (primary) 2	626	698	0.87 (0.78, 0.97)	0.01
Time to distant metastasis (secondary)	301	342	0.86 (0.74, 1.01)	0.06
Overall survival (secondary) - deaths	393	436	0.89 (0.77, 1.02)	0.08
Censored analysis of DFS3	626	649	0.83 (0.74, 0.92)	
Censored analysis of OS3	393	419	0.81 (0.70, 0.93)	

[1] Log rank test, stratified by randomisation option and use of chemotherapy (yes/no)

[2] DFS events: loco-regional recurrence, distant metastasis, invasive contralateral breast cancer, second (non-breast) primary malignancy, death from any cause without a prior cancer event.

[3] Observations in the tamoxifen arm censored at the date of selectively switching to letrozole

Sequential Treatments Analysis (STA)

The Sequential Treatments Analysis (STA) addresses the second primary question of BIG 1-98, namely whether sequencing of tamoxifen and letrozole would be superior to monotherapy. There were no significant differences in DFS, OS, SDFS, or DDFS from switch with respect to monotherapy (Table 6).

Table 6 Sequential treatments analysis of disease-free survival with letrozole as initial endocrine agent (STA switch population)

	N	Number of events[1]	Hazard ratio[2]	(97.5% confidence interval)	Cox model *P*-value
[Letrozole→]Tamoxifen	**1,460**	**254**	**1.03**	**(0.84, 1.26)**	**0.72**
Letrozole	**1,464**	**249**			

1 Protocol definition, including second non-breast primary malignancies, after switch / beyond two years
2 Adjusted by chemotherapy use

There were no significant differences in DFS, OS, SDFS or DDFS in any of the STA from randomisation pairwise comparisons (Table 7).

Table 7 Sequential Treatments Analyses from randomisation (STA-R) of disease-free survival (ITT STA-R population)

	Letrozole→Tamoxifen	Letrozole
Number of patients	1540	1546
Number of patients with DFS events (protocol definition)	330	319
Hazard ratio[1] (99% CI)	1.04 (0.85, 1.27)	
	Letrozole→Tamoxifen	**Tamoxifen[2]**
Number of patients	1540	1548
Number of patients with DFS events (protocol definition)	330	353
Hazard ratio[1] (99% CI)	0.92 (0.75, 1.12)	

[1] Adjusted by chemotherapy use (yes/no)
[2] 626 (40%) patients selectively crossed to letrozole after tamoxifen arm unblinded in 2005

Study D2407
Study D2407 is an open-label, randomised, multicentre post approval safety study designed to compare the effects of adjuvant treatment with letrozole and tamoxifen on bone mineral density (BMD) and serum lipid profiles. A total of 262 patients were assigned either letrozole for 5 years or tamoxifen for 2 years followed by letrozole for 3 years.

At 24 months there was a statistically significant difference in the primary end-point; the lumbar spine BMD (L2-L4) showed a median decrease of 4.1% for letrozole compared to a median increase of 0.3% for tamoxifen.

No patient with a normal BMD at baseline became osteoporotic during 2 years of treatment and only 1 patient with osteopenia at baseline (T score of -1.9) developed osteoporosis during the treatment period (assessment by central review).

The results for total hip BMD were similar to those for lumbar spine but less pronounced.

There was no significant difference between treatments in the rate of fractures – 15% in the letrozole arm, 17% in the tamoxifen arm.

Median total cholesterol levels in the tamoxifen arm were decreased by 16% after 6 months compared to baseline and this decrease was maintained at subsequent visits up to 24 months. In

the letrozole arm, total cholesterol levels were relatively stable over time, giving a statistically significant difference in favour of tamoxifen at each time point.

Extended adjuvant treatment (MA-17)

In a multicentre, double-blind, randomised, placebo-controlled study (MA-17), over 5,100 postmenopausal women with receptor-positive or unknown primary breast cancer who had completed adjuvant treatment with tamoxifen (4.5 to 6 years) were randomised to either Femara or placebo for 5 years.

The primary endpoint was disease-free survival, defined as the interval between randomisation and the earliest occurrence of loco-regional recurrence, distant metastasis, or contralateral breast cancer.

The first planned interim analysis at a median follow-up of around 28 months (25% of patients being followed up for at least 38 months), showed that Femara significantly reduced the risk of breast cancer recurrence by 42% compared with placebo (HR 0.58; 95% CI 0.45, 0.76; *P*=0.00003). The benefit in favour of letrozole was observed regardless of nodal status. There was no significant difference in overall survival: (Femara 51 deaths; placebo 62; HR 0.82; 95% CI 0.56, 1.19).

Consequently, after the first interim analysis the study was unblinded and continued in an open-label fashion and patients in the placebo arm were allowed to switch to Femara for up to 5 years. Over 60% of eligible patients (disease-free at unblinding) opted to switch to Femara. The final analysis included 1,551 women who switched from placebo to Femara at a median of 31 months (range 12 to 106 months) after completion of tamoxifen adjuvant therapy. Median duration for Femara after switch was 40 months.

The final analysis conducted at a median follow-up of 62 months confirmed the significant reduction in the risk of breast cancer recurrence with Femara.

Table 8 Disease-free and overall survival (Modified ITT population)

	Median follow-up 28 months[1]			Median follow-up 62 months		
	Letrozole N=2582	Placebo N=2586	HR (95% CI)[2] *P* value	Letrozole N=2582	Placebo N=2586	HR (95% CI)[2] *P* value
Disease-free survival[3]						
Events	92 (3.6%)	155 (6.0%)	0.58 (0.45, 0.76) 0.00003	209 (8.1%)	286 (11.1%)	0.75 (0.63, 0.89)
4-year DFS rate	94.4%	89.8%		94.4%	91.4%	
Disease-free survival[3], including deaths from any cause						
Events	122 (4.7%)	193 (7.5%)	0.62 (0.49, 0.78)	344 (13.3%)	402 (15.5%)	0.89 (0.77, 1.03)
5 year DFS rate	90.5%	80.8%		88.8%	86.7%	
Distant metastases						
Events	57 (2.2%)	93 (3.6%)	0.61 (0.44, 0.84)	142 (5.5%)	169 (6.5%)	0.88 (0.70, 1.10)
Overall survival						
Deaths	51 (2.0%)	62 (2.4%)	0.82	236	232	1.13

	Median follow-up 28 months[1]			Median follow-up 62 months		
	Letrozole N=2582	Placebo N=2586	HR (95% CI)[2] *P* value	Letrozole N=2582	Placebo N=2586	HR (95% CI)[2] *P* value
			(0.56, 1.19)	(9.1%)	(9.0%)	(0.95, 1.36)
Deaths[4]	- -	- -	- -	236[5] (9.1%)	170[6] (6.6%)	0.78 (0.64, 0.96)

HR = Hazard ratio; CI = Confidence Interval

[1] When the study was unblinded in 2003, 1551 patients in the randomised placebo arm (60% of those eligible to switch – i.e. who were disease-free) switched to letrozole at a median 31 months after randomisation. The analyses presented here ignore the selective crossover.

[2] Stratified by receptor status, nodal status and prior adjuvant chemotherapy.

[3] Protocol definition of disease-free survival events: loco-regional recurrence, distant metastasis or contralateral breast cancer.

[4] Exploratory analysis, censoring follow-up times at the date of switch (if it occurred) in the placebo arm.

[5] Median follow-up 62 months.

[6] Median follow-up until switch (if it occurred) 37 months.

In the MA-17 bone substudy in which concomitant calcium and vitamin D were given, greater decreases in BMD compared to baseline occurred with Femara compared with placebo. The only statistically significant difference occurred at 2 years and was in total hip BMD (letrozole median decrease of 3.8% vs placebo median decrease of 2.0%).

In the MA-17 lipid substudy there were no significant differences between letrozole and placebo in total cholesterol or in any lipid fraction.

In the updated quality of life substudy there were no significant differences between treatments in physical component summary score or mental component summary score, or in any domain score in the SF-36 scale. In the MENQOL scale, significantly more women in the Femara arm than in the placebo arm were most bothered (generally in the first year of treatment) by those symptoms deriving from oestrogen deprivation – hot flushes and vaginal dryness. The symptom that bothered most patients in both treatment arms was aching muscles, with a statistically significant difference in favour of placebo.

Neoadjuvant treatment

A double blind trial (P024) was conducted in 337 postmenopausal breast cancer patients randomly allocated either Femara 2.5 mg for 4 months or tamoxifen for 4 months. At baseline all patients had tumours stage T2-T4c, N0-2, M0, ER and/or PgR positive and none of the patients would have qualified for breast-conserving surgery. Based on clinical assessment there were 55% objective responses in the Femara arm versus 36% for the tamoxifen arm ($P<0.001$). This finding was consistently confirmed by ultrasound (Femara 35% vs tamoxifen 25%, $P=0.04$) and mammography (Femara 34% vs tamoxifen 16%, $P<0.001$). In total 45% of patients in the Femara group versus 35% of patients in the tamoxifen group ($P=0.02$) underwent breast-conserving therapy). During the 4-month pre-operative treatment period, 12% of patients treated with Femara and 17% of patients treated with tamoxifen had disease progression on clinical assessment.

First-line treatment

One controlled double-blind trial was conducted comparing Femara (letrozole) 2.5 mg to tamoxifen 20 mg as first-line therapy in postmenopausal women with advanced breast cancer. In 907 women, letrozole was superior to tamoxifen in time to progression (primary endpoint) and in overall objective response, time to treatment failure and clinical benefit.
The results are summarised in Table 9:

Table 9 Results at a median follow-up of 32 months

Variable	Statistic	Femara N=453	Tamoxifen N=454
Time to progression	Median	9.4 months	6.0 months
	(95% CI for median)	(8.9, 11.6 months)	(5.4, 6.3 months)
	Hazard ratio (HR)	0.72	
	(95% CI for HR)	(0.62, 0.83)	
		P<0.0001	
Objective response rate (ORR)	CR+PR	145 (32%)	95 (21%)
	(95% CI for rate)	(28, 36%)	(17, 25%)
	Odds ratio	1.78	
	(95% CI for odds ratio)	(1.32, 2.40)	
		P=0.0002	

Time to progression was significantly longer, and response rate significantly higher for letrozole irrespective of whether adjuvant anti-oestrogen therapy had been given or not. Time to progression was significantly longer for letrozole irrespective of dominant site of disease. Median time to progression was 12.1 months for Femara and 6.4 months for tamoxifen in patients with soft tissue disease only and median 8.3 months for Femara and 4.6 months for tamoxifen in patients with visceral metastases.

Study design allowed patients to cross over upon progression to the other therapy or discontinue from the study. Approximately 50% of patients crossed over to the opposite treatment arm and crossover was virtually completed by 36 months. The median time to crossover was 17 months (Femara to tamoxifen) and 13 months (tamoxifen to Femara).

Femara treatment in the first-line therapy of advanced breast cancer resulted in a median overall survival of 34 months compared with 30 months for tamoxifen (log-rank test P=0.53, not significant). The absence of an advantage for Femara on overall survival could be explained by the crossover design of the study.

Second-line treatment
Two well-controlled clinical studies were conducted comparing two letrozole doses (0.5 mg and 2.5 mg) to megestrol acetate and to aminoglutethimide, respectively, in postmenopausal women with advanced breast cancer previously treated with anti-oestrogens.

Time to progression was not significantly different between letrozole 2.5 mg and megestrol acetate (*P*=0.07). Statistically significant differences were observed in favour of letrozole 2.5 mg compared to megestrol acetate in overall objective tumour response rate (24% vs 16%, *P*=0.04), and in time to treatment failure (*P*=0.04). Overall survival was not significantly different between the 2 arms (*P*=0.2).

In the second study, the response rate was not significantly different between letrozole 2.5 mg and aminoglutethimide (*P*=0.06). Letrozole 2.5 mg was statistically superior to aminoglutethimide for time to progression (*P*=0.008), time to treatment failure (*P*=0.003) and overall survival (*P*=0.002).

Male breast cancer
Use of Femara in men with breast cancer has not been studied.

5.2 Pharmacokinetic properties

Absorption
Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability: 99.9%). Food slightly decreases the rate of absorption (median t_{max} 1 hour fasted versus 2 hours fed; and mean C_{max} 129 ± 20.3 nmol/litre fasted versus 98.7 ± 18.6 nmol/litre fed) but the extent of absorption (AUC) is not changed. The minor effect on the absorption rate is not considered to be of clinical relevance, and therefore letrozole may be taken without regard to mealtimes.

Distribution
Plasma protein binding of letrozole is approximately 60%, mainly to albumin (55%). The concentration of letrozole in erythrocytes is about 80% of that in plasma. After administration of 2.5 mg ^{14}C-labelled letrozole, approximately 82% of the radioactivity in plasma was unchanged compound. Systemic exposure to metabolites is therefore low. Letrozole is rapidly and extensively distributed to tissues. Its apparent volume of distribution at steady state is about 1.87 ± 0.47 l/kg.

Biotransformation
Metabolic clearance to a pharmacologically inactive carbinol metabolite is the major elimination pathway of letrozole (CL_m = 2.1 l/h) but is relatively slow when compared to hepatic blood flow (about 90 l/h). The cytochrome P450 isoenzymes 3A4 and 2A6 were found to be capable of converting letrozole to this metabolite. Formation of minor unidentified metabolites and direct renal and faecal excretion play only a minor role in the overall elimination of letrozole. Within 2 weeks after administration of 2.5 mg ^{14}C-labelled letrozole to healthy postmenopausal volunteers, 88.2 ± 7.6% of the radioactivity was recovered in urine and 3.8 ± 0.9% in faeces. At least 75% of the radioactivity recovered in urine up to 216 hours (84.7 ± 7.8% of the dose) was attributed to the glucuronide of the carbinol metabolite, about 9% to two unidentified metabolites, and 6% to unchanged letrozole.

Elimination
The apparent terminal elimination half-life in plasma is about 2 to 4 days. After daily administration of 2.5 mg steady-state levels are reached within 2 to 6 weeks. Plasma concentrations at steady state are approximately 7 times higher than concentrations measured after a single dose of 2.5 mg, while they are 1.5 to 2 times higher than the steady-state values predicted from the concentrations measured after a single dose, indicating a slight non-linearity in the pharmacokinetics of letrozole upon daily administration of 2.5 mg. Since steady-state levels are maintained over time, it can be concluded that no continuous accumulation of letrozole occurs.

Linearity/non-linearity
The pharmacokinetics of letrozole were dose proportional after single oral doses up to 10 mg (dose range: 0.01 to 30 mg) and after daily doses up to 1.0 mg (dose range: 0.1 to 5mg). After a

30 mg single oral dose there was a slightly dose over-proportional increase in AUC value. The dose over-proportionality is likely to be the result of a saturation of metabolic elimination processes. Steady levels were reached after 1 to 2 months at all dosage regimens tested (0.1-5.0 mg daily).

Special populations
Elderly
Age had no effect on the pharmacokinetics of letrozole.

Renal impairment
In a study involving 19 volunteers with varying degrees of renal function (24-hour creatinine clearance 9-116 ml/min) no effect on the pharmacokinetics of letrozole was found after a single dose of 2.5 mg. In addition to the above study assessing the influence of renal impairment on letrozole, a covariate analysis was performed on the data of two pivotal studies (Study AR/BC2 and Study AR/BC3). Calculated creatinine clearance (CLcr) [Study AR/BC2 range: 19 to 187 mL/min; Study AR/BC3 range: 10 to 180 mL/min] showed no statistically significant association between letrozole plasma trough levels at steady-state (Cmin). Furthermore, data of Study AR/BC2 and Study AR/BC3 in second-line metastatic breast cancer showed no evidence of an adverse effect of letrozole on CLcr or an impairment of renal function.

Therefore, no dose adjustment is required for patients with renal impairment (CLcr $\geq$10 mL/min). Little information is available in patients with severe impairment of renal function (CLcr <10 mL/min).

Hepatic impairment
In a similar study involving subjects with varying degrees of hepatic function, the mean AUC values of the volunteers with moderate hepatic impairment (Child-Pugh B) was 37% higher than in normal subjects, but still within the range seen in subjects without impaired function. In a study comparing the pharmacokinetics of letrozole after a single oral dose in eight male subjects with liver cirrhosis and severe hepatic impairment (Child-Pugh C) to those in healthy volunteers (N=8), AUC and $t_{½}$ increased by 95 and 187%, respectively. Thus, Femara should be administered with caution to patients with severe hepatic impairment and after consideration of the risk/benefit in the individual patient.

5.3 Preclinical safety data

In a variety of preclinical safety studies conducted in standard animal species, there was no evidence of systemic or target organ toxicity.

Letrozole showed a low degree of acute toxicity in rodents exposed up to 2000 mg/kg. In dogs letrozole caused signs of moderate toxicity at 100 mg/kg.

In repeated-dose toxicity studies in rats and dogs up to 12 months, the main findings observed can be attributed to the pharmacological action of the compound. The no-adverse-effect level was 0.3 mg/kg in both species.

Oral administration of letrozole to female rats resulted in decreases in mating and pregnancy ratios and increases in pre-implantation loss.

Both *in vitro* and *in vivo* investigations of letrozole's mutagenic potential revealed no indications of any genotoxicity.

In a 104-week rat carcinogenicity study, no treatment-related tumours were noted in male rats. In female rats, a reduced incidence of benign and malignant mammary tumours at all the doses of letrozole was found.

In a 104-week mouse carcinogenicity study, no treatment-related tumours were noted in male mice. In female mice, a generally dose-related increase in the incidence of benign ovarian granulosa theca cell tumours was observed at all doses of letrozole tested. These tumours were considered to be related to the pharmacological inhibition of oestrogen synthesis and may be due to increased LH resulting from the decrease in circulating oestrogen.

Letrozole was embryotoxic and foetotoxic in pregnant rats and rabbits following oral administration at clinically relevant doses. In rats that had live foetuses, there was an increase in the incidence of foetal malformations including domed head and cervical/centrum vertebral fusion. An increased incidence of foetal malformations was not seen in the rabbit. It is not known whether this was an indirect consequence of the pharmacological properties (inhibition of oestrogen biosynthesis) or a direct drug effect (see sections 4.3 and 4.6).

Preclinical observations were confined to those associated with the recognised pharmacological action, which is the only safety concern for human use derived from animal studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet content: Lactose monohydrate, Cellulose microcrystalline, Maize starch, Sodium starch glycolate, Magnesium stearate and Silica colloidal anhydrous.

Coating: Hypromellose (E464), Talc, Macrogol 8000, Titanium dioxide (E 171) and Iron oxide yellow (E 172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PE/PVDC/aluminium blisters
Packs of 10 (1x10), 14 (1x14), 28 (2x14), 30 (3x10), 100 (10 x 10) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

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Ballsbridge, Dublin 4,
Ireland.

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