AUSTRALIAN PRODUCT INFORMATION – FEMARA® (LETROZOLE)

1 NAME OF THE MEDICINE

Letrozole

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Femara is available as coated tablets containing 2.5 mg letrozole.

Excipients of known effect: lactose, galactose, and sulfites.

For the full list of excipients, section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Tablet containing 2.5mg letrozole; round, film coated, dark yellow, marked FV on one side and CG on the other; in blister packs of 10 and 30 tablets.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the treatment of postmenopausal women with hormone receptor positive breast cancer (see section 5.1 Pharmacodynamic Properties, Clinical Trials).

The safety and efficacy of neoadjuvant use of letrozole has not been established. Letrozole is not indicated in hormone receptor negative disease.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

The recommended dose of Femara is one 2.5 mg tablet daily.

In the adjuvant setting, treatment should continue for 5 years or until tumour relapse occurs, whichever comes first.

In the extended adjuvant setting, the optimal treatment duration with Femara is not known. The planned duration of treatment in the pivotal study was 5 years. However, at the time of the analysis, the median duration of treatment was 24 months, 25% of patients were treated for at least three years and less than 1% of patients were treated for the planned 5 years. The median duration of follow up was 28 months. Treatment should be discontinued at tumour relapse.

In the adjuvant setting the median duration of treatment was 25 months, 73% of the patients were treated for more than 2 years, 22% of the patients for more than 4 years. The median

duration of follow up was 30 months (the efficacy data mentioned in “Clinical Trials” are based on the Primary Core Analysis with a median duration of follow up of 26 months).

In patients with metastatic disease, treatment with Femara should continue until tumour progression is evident.

Elderly patients

No dose adjustment is required.

Patients with hepatic / renal impairment

No dosage adjustment of Femara is required for patients with mild renal impairment (creatinine clearance ≥ 30 mL/min). Insufficient data are available to justify dose advice in cases of renal insufficiency with creatinine clearance less than 30 mL/min. Insufficient data are available to justify dose advice in patients with severe hepatic insufficiency. Patients with severe hepatic impairment (Child-Pugh score C) should be kept under close supervision (see section 5.2 Pharmacokinetic properties and section 4.4 Special warnings and precautions for use).

Children

Femara is not recommended for use in children and adolescents. The safety and efficacy of Femara in children and adolescents aged up to 18 years have not been established. Limited data are available and no recommendation on a posology can be made.

Method of administration

Femara should be taken orally. A missed dose should be taken as soon as the patient remembers. However, if it is almost time for the next dose, 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.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients

Premenopausal endocrine status; pregnancy, lactation (see section 4.4 Special warnings and precautions for use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use with Caution in the Following Circumstances

Use in renal impairment:

Femara has not been investigated in patients with creatinine clearance < 10 mL/min nor in a sufficient number of patients with a creatinine clearance less than 30 mL/min. The potential

risk/benefit to such patients should be carefully considered before administration of Femara. As letrozole is weakly bound to plasma proteins (see section 5.2 Pharmacokinetics), it is anticipated that it could be removed from circulation by dialysis. Similar caution should be exercised in patients with severe hepatic insufficiency.

Use in hepatic impairment:

In patients with severe hepatic cirrhosis (Child-Pugh score 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 Pharmacokinetics).

Menopausal status

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

Interactions

Co-administration of Femara with tamoxifen, other anti-estrogens or estrogen-containing therapies should be avoided as these substances may diminish the pharmacological action of letrozole. The mechanism of this interaction is unknown.

Bone effects

Osteoporosis and/or bone fractures have been reported with the use of letrozole. Therefore, monitoring of overall bone health is recommended during treatment (see section 4.8 Adverse effects (Undesirable effects) & section 5.1 Pharmacodynamic properties Clinical trials).

Tendon disorders

The use of third generation aromatase inhibitors, including letrozole, were found to be associated with tendonitis and tenosynovitis in randomised controlled trials. Tendon rupture was found to be a potential risk. Tendonitis and tenosynovitis were estimated to be of uncommon occurrence, and tendon rupture of rare occurrence. Monitor patients for signs and symptoms of tendon disorders during treatment with FEMARA.

Paediatric Use

Refer to section 4.2 Dose and method of administration.

Use in the Elderly

Refer to section 4.2 Dose and method of administration.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

To date, there are minimal data on the interaction between letrozole and other drugs.

Additionally, in a large clinical trial there was no evidence of clinically relevant interaction in patients receiving other commonly prescribed drugs (e.g. benzodiazepines; barbiturates; NSAIDs such as diclofenac sodium and ibuprofen; paracetamol; frusemide; omeprazole).

Letrozole is mainly metabolized in the liver and the cytochrome P450 enzymes CYP3A4 and CYP2A6 mediate the metabolic clearance of letrozole. Therefore, the systemic elimination of letrozole may be influenced by drugs known to affect the CYP3A4 and CYP2A6.

Drugs that may increase Letrozole serum concentrations

Inhibitors of CYP3A4 and CYP2A6 activities could decrease the metabolism of letrozole and thereby increase plasma concentrations of letrozole. The concomitant administration of medications that strongly inhibit these enzymes (strong CYP3A4 inhibitors: including but not limited to ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, and telithromycin; CYP2A6 (e.g. methoxsalen) may increase exposure to letrozole. Therefore caution is recommended in patients for whom strong CYP3A4 and CYP2A6 inhibitors are indicated.

Drugs that may decrease Letrozole serum concentrations

Inducers of CYP3A4 activity could increase the metabolism of letrozole and thereby decrease plasma concentrations of letrozole. The concomitant administration of medications that induce CYP3A4 (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital, and St. John's Wort) may reduce exposure to letrozole. Therefore caution is recommended in patients for whom strong CYP3A4 inducers are indicated. No drug inducer is known for CYP2A6.

Co-administration of Femara (2.5mg) and tamoxifen 20 mg daily resulted in a reduction of letrozole plasma levels by 38% on average. The mechanism of this interaction is unknown.

There is limited clinical experience to date on the use of Femara in combination with anti-cancer agents other than tamoxifen.

Drugs that may have their systemic serum concentrations altered by Letrozole

In vitro, letrozole inhibits the cytochrome P450 isoenzymes CYP2A6 and, moderately, CYP2C19, but the clinical relevance is unknown. Caution is therefore indicated when giving letrozole concomitantly with medicinal products whose elimination is mainly dependent on CYP2C19 and whose therapeutic index is narrow (e.g. phenytoin, clopidrogel). No substrate with a narrow therapeutic index is known for CYP2A6.

Clinical interaction studies with cimetidine (a known non-specific inhibitor of CYP2C19 and CYP3A4 and warfarin (sensitive substrate for CYP2C9 with a narrow therapeutic window and

commonly used as co-medication in the target population of letrozole) indicated that the coadministration of Femara with these drugs does not result in clinically significant drug interactions.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In rats treated with letrozole beginning on day 7 post-partum for 9 weeks, mating and fertility were decreased at all doses (0.003-0.3 mg/kg/day; below and similar to the human exposure at 2.5 mg/day). The treated rats also displayed delayed sexual maturation, prolonged diestrus and histological changes of reproductive organs (see section 5.3 Preclinical safety data).

Chronic studies indicated stromal hyperplasia of the ovaries and uterine atrophy in rats administered oral doses equal to or greater than 0.3 mg/kg/day (approximately equivalent to human exposure at 2.5 mg/day, based on AUC). In addition, ovarian follicular atrophy and uterine atrophy were observed in chronic studies of female dogs administered doses equal to or greater than 0.03 and 0.3 mg/kg/day respectively (less than and approximately equivalent to human exposure at 2.5 mg/day).

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

Women of child-bearing potential

There have been post-marketing reports of spontaneous abortions and congenital anomalies in infants of mothers who have taken Femara. The physician needs to discuss the necessity of adequate contraception with women who have the potential to become pregnant including women who are perimenopausal or who recently became postmenopausal, until their postmenopausal status is fully established.

Use in pregnancy

Category D

Treatment of pregnant rats with letrozole at oral doses of 0.03 mg/kg/day during organogenesis was associated with a slight increase in the incidence of fetal malformation among the animals treated. It was not possible to show whether this was an indirect consequence of the pharmacological properties (inhibition of oestrogen biosynthesis) or a direct effect of letrozole in its own right. At doses of 0.003 mg/kg and above, higher incidences of resorptions and dead fetuses were also reported. These effects are consistent with the disruption of oestrogen-dependent events during pregnancy and are not unexpected with a drug of this class. No peri/postnatal studies have been conducted in animals.

Femara is contraindicated during pregnancy (see section 4.3 Contraindications). Isolated cases of birth defects (labial fusion, ambiguous genitalia) have been reported in pregnant women exposed to Femara.

Use in lactation.

Femara is contraindicated during lactation. It is not known if letrozole is excreted in human or animal milk (see section 4.3 Contraindications).

4.7 EFFECTS ON 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Femara was generally well tolerated across all studies as first-line and second-line treatment for advanced breast cancer, as adjuvant treatment of early breast cancer, and as extended adjuvant treatment of early breast cancer in women who have received prior standard tamoxifen therapy. Approximately one third of the patients treated with Femara in the metastatic setting, and approximately 80% of the patients in the adjuvant setting (both Femara and tamoxifen arms, at a median treatment duration of 60 months), and extended adjuvant setting (both Femara and placebo arms, at a median treatment duration of 60 months for Femara) can be expected to experience adverse reactions. Generally, the observed adverse reactions are mainly mild or moderate in nature, and many are associated with oestrogen deprivation.

The most frequently reported adverse reactions in the clinical studies were hot flushes, arthralgia, nausea and fatigue. Many adverse reactions can be attributed to either the normal pharmacological consequences of oestrogen deprivation (e.g. hot flushes, alopecia and vaginal bleeding).

The following adverse events, not reported in the advanced or clinical trials, were noted in the extended adjuvant setting: arthralgia/arthritis, osteoporosis and bone fractures (see section 5.1 Pharmacodynamic properties Clinical trials - Extended adjuvant treatment of early breast cancer).

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

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: very common ≥10%, common ≥1% to <10%; uncommon ≥0.1% to <1%; rare ≥0.01% to <0.1%; very rare <0.01%, not known (cannot be estimated from the available data).

Table 1 Adverse drug reactions

Infections and infestations	
Uncommon:	Urinary tract infection.
Neoplasms benign and malignant (including cysts and polyps)	
Uncommon:	Tumour pain (1).
Blood and the lymphatic system disorders	
Uncommon:	Leucopenia.
Immune system disorders	
Very rare:	Anaphylactic reaction.
Metabolism and nutrition disorders	
Very common:	Hypercholesterolaemia.
Common:	Anorexia, appetite increase.
Psychiatric disorders	
Common:	Depression.
Uncommon:	Anxiety (including nervousness), irritability.
Nervous system disorders	
Common:	Headache, dizziness, vertigo.
Uncommon:	Somnolence, insomnia, memory impairment, dysaesthesia (including paraesthesia, hypoaesthesia), taste disturbance, cerebrovascular accident, carpal tunnel syndrome.
Eye disorders	
Uncommon	Cataract, eye irritation, blurred vision.
Cardiac disorders	
Common	Palpitations
Uncommon:	Tachycardia, ischemic cardiac events (2, 3) (including new or worsening angina, angina requiring surgery, myocardial infarction and myocardial ischemia).
Vascular disorders	
Very common:	Hot flushes.
Common:	Hypertension.
Uncommon:	Thrombophlebitis (including superficial and deep vein thrombophlebitis).
Rare:	Pulmonary embolism, arterial thrombosis, cerebrovascular infarction.
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Dyspnoea, cough.
Gastrointestinal disorders	
Common:	Nausea, vomiting, dyspepsia, constipation, diarrhoea, abdominal pain.
Uncommon:	Stomatitis, dry mouth.
Hepato-biliary disorders	
Uncommon:	Increased hepatic enzymes, hyperbilirubinaemia, jaundice
Very rare:	Hepatitis.

Skin and subcutaneous tissue disorders	
Very common:	Increased sweating.
Common:	Alopecia, dry skin, rash (including erythematous, maculopapular, psoriaform and vesicular rash).
Uncommon:	Pruritus, urticaria.
Very rare:	Angioedema, toxic epidermal necrolysis, erythema multiforme.
Musculoskeletal, connective tissue and bone disorders	
Very common:	Arthralgia.
Common:	Myalgia, bone pain, osteoporosis, bone fractures, arthritis, back pain
Not known:	Trigger finger, tendonitis, tenosynovitis, tendon rupture (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
Renal and urinary disorders	
Uncommon	Increased urinary frequency.
Reproductive system and breast disorders	
Common:	Vaginal bleeding.
Uncommon	Vaginal discharge, vaginal dryness, breast pain.
General disorders and administration site conditions	
Very common:	Fatigue (including aesthenia and malaise).
Common:	Peripheral oedema, chest pain
Uncommon:	General oedema, pyrexia, mucosal dryness, thirst.
Investigations	
Common:	Weight increase.
Uncommon:	Weight loss
Injury, poisoning and procedural complication	
Common (4)	Fall (5)

(1) Adverse drug reactions reported only in the metastatic setting.
(2) In the adjuvant setting, irrespective of causality, the following adverse events occurred in the Femara and tamoxifen groups respectively: thromboembolic events (2.1% vs. 3.6%), angina pectoris (1.1% vs. 1.0%), myocardial infarction (1.0% vs. 0.5%) and cardiac failure (0.8% vs., 0.5%).
(3) In the extended adjuvant setting, at a median treatment duration of 60 months for letrozole and 37 months for placebo, the following AEs were reported for Femara and placebo (excluding all switches to Femara) respectively: new or worsening angina (1.4% vs. 1.0%); angina requiring surgery (0.8% vs. 0.6%); myocardial infarction (1.0% vs. 0.7%); thromboembolic event (0.9% vs. 0.3%); stroke/TIA (1.5% vs. 0.8%).
(4) Frequency determined based on FACE study data
(5) In some cases fall was reported as a consequence of other adverse events such as dizziness and vertigo

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Isolated cases of overdosage with Femara have been reported. No specific treatment for overdosage is known. Treatment should be symptomatic and supportive.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Non-steroidal aromatase inhibitor (inhibitor of oestrogen biosynthesis); antineoplastic agent.

Pharmacodynamics

Mechanism of action

The elimination of oestrogen-mediated stimulatory effects is a prerequisite for tumour response in cases where the growth of tumour tissue depends on the presence of oestrogens. In postmenopausal women, oestrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens - primarily androstenedione and testosterone - to oestrone (E1) and oestradiol (E2). The suppression of oestrogen biosynthesis in peripheral tissues and the cancer tissue itself can, therefore, be achieved by specifically inhibiting the aromatase enzyme.

Letrozole is a non-steroidal aromatase inhibitor. Data suggest it inhibits the aromatase enzyme by competitively binding to the haem of the cytochrome P450 subunit of the enzyme, resulting in a reduction of oestrogen biosynthesis in all tissues.

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

In postmenopausal patients with advanced breast cancer, daily doses of 0.1 to 5 mg letrozole suppressed plasma concentrations 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 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-hydroxy-progesterone, ACTH or in plasma renin activity among postmenopausal patients treated with a daily dose of

0.1 to 5 mg letrozole. The ACTH stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0.1, 0.25, 0.5, 1, 2.5 and 5 mg letrozole 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, 0.5 and 2.5 mg single doses of letrozole or in plasma concentrations of androstenedione among postmenopausal patients treated with daily doses of 0.1 to 5 mg, indicating that the blockade of oestrogen biosynthesis does not lead to accumulation of androgenic precursors. Plasma levels of LH and FSH were not affected by letrozole in patients, nor was thyroid function as evaluated by TSH, T4 and T3 uptake.

Clinical trials

Adjuvant treatment of early breast cancer

Study BIG 1-98

BIG 1-98, a multi-centre, double-blind, randomised study was conducted in over 8000 postmenopausal women with resected receptor-positive early breast cancer. In this study, patients were randomly assigned to one of the following arms:

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

This study was designed to investigate two primary questions: whether Femara for 5 years was superior to tamoxifen for 5 years (Primary Core Analysis and Monotherapy Arms Analysis and whether switching endocrine treatments at 2 years was superior to continuing the same agent for a total of 5 years (Sequential Treatments Analysis).

The protocol specified efficacy endpoints were disease free survival (DFS), overall survival (OS) and systemic disease-free survival (SDFS). The protocol specified primary efficacy endpoint of DFS was defined as the interval between date of randomisation and earliest confirmed invasive loco-regional recurrence, distant metastasis, invasive contralateral breast cancer, second invasive (non-breast) primary cancer, or death from any cause without a prior cancer event. The protocol specified secondary efficacy endpoint of OS was defined as the interval from randomisation to death from any cause. The protocol specified secondary efficacy endpoint of SDFS was defined as the interval from randomisation to systemic relapse, distant metastasis, appearance of a second (non-breast) primary cancer, or death from any cause, whichever occurred first (i.e. excluding loco regional recurrences in the ipsilateral or

contralateral breast). In addition, secondary efficacy endpoints specified in the statistical analysis plan prior to the end of enrollment and prior to an interim analysis included time to distant metastases and time to invasive contralateral breast cancer.

Efficacy results at a median follow-up of 26 months:

Data in Table 2 reflects results of the Primary Core Analysis (PCA) including data from non-switching arms (arms A and B) together with data truncated 30 days after the switch in the two switching arms (arms C and D). This analysis was conducted at a median treatment duration of 24 months and a median follow-up of 26 months. Femara for 5 years was superior to tamoxifen for efficacy endpoints of disease free survival (protocol specified), time to distant metastases, and systemic disease free survival, but not for the efficacy endpoints of overall survival and invasive contralateral breast cancer.

Table 2 Disease-free and overall survival (PCA ITT population) at a median follow-up of 26 months

	Femara N=4003	**Tamoxifen N=4007**	**Hazard ratio (95% CI)**	***P-Value*[1]**
Disease-free survival (primary) - events (protocol definition, total)	351	428	0.81 (0.70, 0.93)	0.0030
Time to distant metastases (secondary)	184	249	0.73 (0.60, 0.88)	0.0012
Overall survival (secondary) – number of deaths (total)	166	192	0.86 (0.70, 1.06)	0.1546
Systemic disease-free survival SDFS (secondary)	323	383	0.83 (0.72, 0.97)	0.0172
Contralateral breast disease (invasive) secondary)	19	31	0.61 (0.35, 1.08)	0.0910

CI = confidence interval, DDFS: time from randomisation to the earliest occurrence of a distant metastasis
SDFS: time from randomisation to systemic relapse, metastasis, appearance of a second (non-breast) primary cancer, or death form any cause, whichever occurred first
[1] Logrank test, stratified by randomisation option and use of prior adjuvant chemotherapy

MAA efficacy results at a median follow-up of 73 months:

The Monotherapy Arms Analysis (MAA) which include data for the monotherapy arms only provides the clinically appropriate long-term update of the efficacy of Femara monotherapy compared to tamoxifen monotherapy (Table 3). In 2005, based on the PCA data presented in Table 2 and on recommendations by the independent Data Monitoring Committee, the tamoxifen monotherapy arms were unblinded and patients were allowed to cross over to Femara. 26 % of patients randomized to tamoxifen elected to cross over to Femara – including a very small number of patients who crossed over to other aromatase inhibitors. To explore

the impact of this selective crossover, analyses censoring DFS and OS follow-up times at the date of the selective crossover (in the tamoxifen arm) were conducted, and these analyses as well as the ITT analyses for selective endpoints disregarding selective crossover from tamoxifen to letrozole are summarised for the MAA (Table 3).

At a median follow-up of 73 months and a median treatment duration of 60 months, the risk of a DFS event was significantly reduced with Femara compared with tamoxifen (MAA ITT analysis: HR 0.88; 95% CI 0.78, 0.99; P=0.03; confirming the 2005 PCA results. Analysis of DFS taking account of the selective crossover shows similar benefit (HR 0.85; 95% CI 0.75, 0.96). Similarly, the updated analysis confirmed the superiority of Femara in reducing the risk of distant disease free survival events (HR 0.87, 0.76, 1.00) as well as the risk of reducing distant metastases (HR 0.85; 95% CI 0.72, 1.00). Additionally, overall survival trended towards significance in the ITT analysis. Analysis of overall survival taking account of the selective crossover shows a significantly greater benefit (HR 0.82 0.70, 0.96) in favour of Femara.

Table 3 Disease-free and overall survival (MAA ITT population) at a median follow up of 73 months

	Femara N=2463	**Tamoxifen N=2459**	**Hazard Ratio (95 % CI)**	***P-Value*[1]**
Disease-free survival (primary) - events (protocol definition, total)	509	565	0.88 (0.78, 0.99)	0.03
Time to distant metastases (secondary)	257	298	0.85 (0.72, 1.00)	0.045
Distant disease-free survival (metastases) (secondary)	385	432	0.87 (0.76, 1.00)	0.049
Overall survival (secondary) - number of deaths (total)	303	343	0.87 (0.75, 1.02)	0.08
Systemic disease-free survival (secondary)	465	512	0.89 (0.79, 1.01)	0.065
Contralateral breast cancer (invasive) (secondary)	34	44	0.76 (0.49, 1.19)	0.2
Censored analysis of DFS [2]	509	543	0.85 (0.75, 0.96)	-
Censored analysis of Overall survival [2]	303	338	0.82 (0.70, 0.96)	-

CI = confidence interval,

[1] Logrank test, stratified by randomisation option and use of prior adjuvant chemotherapy

[2] Analysis censoring observation times at date of selective crossover if crossover occurred

Sequential Treatments Analyses:

The Sequential Treatments Analysis (STA) addresses the second primary question of the study. The primary analysis for the STA was from switch (or equivalent time-point in monotherapy groups) + 30 days (STA-S) with a two-sided test applied to each pair-wise comparison at the 2.5% level. These analyses were conducted at a median follow-up of 43 months after switch. Additional, exploratory analyses were conducted from randomisation (STA-R) at a median follow up of 67 months, with the results for each comparison summarised by hazard ratios and 99% confidence intervals.

At a median follow up of 43 months after switch, there were no significant differences in any endpoint from switch in the Sequential Treatments Analysis with respect to either monotherapy (e.g. [Tamoxifen 2 years followed by] Femara 3 years versus tamoxifen beyond 2 years, DFS HR 0.85; 97.5% CI 0.67, 1.09 and [Femara 2 years followed by] tamoxifen 3 years versus Femara beyond 2 years, DFS HR 0.92; 97.5% CI 0.71, 1.17). At a median follow up of 67 months from randomisation, there were no significant differences in any endpoint from randomisation in the Sequential Treatments Analysis (e.g. tamoxifen 2 years followed by Femara 3 years versus Femara 5 years, DFS HR 1.05; 99% CI 0.84, 1.32; Femara 2 years followed by tamoxifen 3 years versus Femara 5 years, DFS HR 0.96; 99% CI 0.76, 1.21). There was no evidence that a sequence of Femara and tamoxifen was superior to Femara alone given for 5 years.

Safety data at a median treatment duration of 60 months derived from MAA:

In study BIG-98 at a median treatment duration of 60 months, the side effects seen were consistent with the safety profile of the drug. Certain adverse reactions were prospectively specified for analysis, based on the known pharmacologic properties and side effect profiles of the two drugs.

Adverse events were analyzed irrespective of drug relationship. Most adverse events reported (approximately 75% of patients reporting 1 or more AE) were Grade 1 and Grade 2 applying the CTC criteria Version 2.0/ CTCAE, version 3.0. When considering all grades during study treatment, a statistically significantly higher incidence of events was seen for Femara compared to tamoxifen regarding hypercholesterolemia (52% vs. 29%), fractures (10.1% vs. 7.1%), myocardial infarctions (1.0% vs. 0.5%), osteoporosis (5.1% vs. 2.7%) and arthralgia (25.2% vs. 20.4%), vulvovaginal dryness (3.6% vs. 1.7%).

A statistically significantly higher incidence was seen for tamoxifen compared to Femara regarding hot flushes (38% vs. 33%), night sweating (17% vs. 15%), vaginal bleeding (13% vs. 5.2%), constipation (2.9% vs. 2.0%), thromboembolic events (3.6% vs. 2.1%), endometrial hyperplasia/cancer (2.3% vs. 0.2%), and endometrial proliferation disorders (3.5% vs. 0.6%).

Adjuvant Therapy in Early Breast Cancer, Study D2407:

Study D2407 is a phase III, open-label, randomised, multicentre study designed to compare the effects of adjuvant treatment with letrozole to tamoxifen on bone mineral density (BMD), bone markers and fasting serum lipid profiles. A total of 262 postmenopausal women with hormone sensitive resected primary breast cancer were randomly assigned to either letrozole 2.5 mg daily for 5 years or tamoxifen 20 mg daily for 2 years followed by 3 years of letrozole 2.5 mg daily.

The primary objective was to compare the effects on lumbar spine (L2-L4) BMD of letrozole versus tamoxifen, evaluated as percent change from baseline lumbar spine BMD at 2 years.

At 24 months, the lumbar spine (L2-L4) BMD showed a median decrease of 4.1% in the letrozole arm compared to a median increase of 0.3% in the tamoxifen arm (difference = 4.4%). At 2 years, overall the median difference in lumbar spine BMD change between letrozole and tamoxifen was statistically significant in favour of tamoxifen (P<0.0001). The current data indicates that no patient with a normal BMD at baseline became osteoporotic at year 2 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 BMD. The differences, however, were less pronounced. At 2 years, a significant difference in favour of tamoxifen was observed in the overall BMD safety population and all stratification categories (P<0.0001). During the 2 year period, fractures were reported by 20 patients (15%) in the letrozole arm, and 22 patients (17%) in the tamoxifen arm.

In the tamoxifen arm, the median total cholesterol levels decreased by 16% after 6 months compared to baseline; a similar decrease was also observed at subsequent visits up to 24 months. In the letrozole arm, the median total cholesterol levels were relatively stable over time, with no significant increase at a single visit. The differences between the 2 arms were statistically significant in favour of tamoxifen at each time point (P<0.0001).

Extended adjuvant treatment of early breast cancer:

A multi-centre, double-blind, randomised, placebo-controlled study (CFEM345G MA-17) was conducted in over 5100 postmenopausal patients with receptor-positive or unknown primary breast cancer. In this study, patients who had remained disease-free after completion of adjuvant treatment with tamoxifen (4.5 to 6 years) were randomly assigned either Femara or placebo.

The planned duration of treatment for patients in the study was 5 years but the trial was unblinded early because of an interim analysis showing a favourable Femara effect. At the time of unblinding, women had been followed for a median of 28 months (25% of the patients had been followed-up for up to 38 months). The primary analysis showed that Femara significantly reduced the risk of recurrence by 42% compared with placebo (hazard ratio 0.58; P=0.00003). The statistically significant benefit in disease free survival (DFS) in favour of Femara was observed regardless of nodal status – node negative, hazard ratio 0.48, P=0.002; node positive, hazard ratio 0.61, P=0.002.

The independent Data and Safety Monitoring Committee (DSMC) recommended that women who were disease-free in the placebo arm be allowed to switch to Femara for up to 5 years, when the study was unblinded in 2003. The study protocol was duly amended, implementing the DSMC recommendation: 60% of the eligible patients in the placebo arm opted to switch to Femara, while the remaining patients opted to have no further treatment but agreed to continue to be monitored. The selective switch to Femara severely compromised further

comparative analyses of efficacy and safety – in the final, close-out analysis after a median treatment duration of 5 years for Femara, 64% of the randomised placebo arm total follow-up patient-years was actually accrued under Femara, not placebo.

In the updated, final analysis conducted in 2008, 1551 women opted to switch from placebo to Femara, at a median 31 months after completion of adjuvant tamoxifen therapy. Median duration of Femara after switch was 40 months.

All significance levels in the 2008 analysis are provided for information purposes only, not for inference. No adjustment has been made for multiple updates or for multiple endpoints. Analyses of efficacy endpoints "ignoring the switch" compare the randomised Femara arm with a control arm in which follow-up was approximately one third placebo, two-thirds Femara. Median treatment duration for Femara was 60 months; in the placebo arm, median duration of placebo until switch (if a switch occurred) was 37 months.

The updated final analysis, conducted at a median follow-up of 62 months, confirmed the significant reduction in the risk of breast cancer recurrence with Femara compared with placebo, despite 60% of women in the placebo arm switching to Femara after the study was unblinded. The protocol-specified 4-year DFS rate was identical in the Femara arm for both the 2004 and 2008 analyses, confirming the stability of the data and robust effectiveness of Femara long-term. In the placebo arm, the impact of the selective switch to Femara is seen in the increase in 4-year DFS rate and in the apparent dilution in treatment difference.

In the original analysis, for the secondary endpoint overall survival (OS) a total 113 deaths were reported (51 Femara, 62 placebo). Overall, there was no significant difference between treatments in OS (hazard ratio 0.82; P=0.29). In node positive disease, Femara significantly reduced the risk of all-cause mortality by approximately 40% (hazard ratio 0.61; P=0.035), whereas no significant difference was seen in patients with node negative disease patients (hazard ratio 1.36; P=0.385), in patients with prior chemotherapy, or in patients with no prior chemotherapy. Tables 4 and 5 summarise the results.

Table 4 Disease-free and overall survival (Modified ITT population)

	2004 analysis – median follow-up 28 months				2008 final update analysis[1] – median follow-up 62 months	
	Letrozole	**Placebo**	**HR (95% CI)[2]**	**Letrozole**	**Placebo**	**HR (95% CI)[2]**
	N=2582	**N=2586**	***P value***	**N=2582**	**N=2586**	***P value***
Disease-free survival (protocol definition)[3]						
Events	92 (3.6%)	155 (6.0%)	0.58 (0.45, 0.76) 0.0003	209 (8.1%)	286 (11.1%)	0.75 (0.63, 0.89) 0.001
4-year DFS rate	94.4%	89.8%		94.4%	91.4%	
Disease-free survival including deaths from any cause						
Events	122 (4.7%)	193 (7.5%)	0.62 (0.49, 0.78) 0.0003	344 (13.3%)	402 (15.5%)	0.89 (0.77, 1.03) 0.120
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) 0.003	142 (5.5%)	169 (6.5%)	0.88 (0.70, 1.10) 0.246
Overall survival						
Deaths	51 (2.0%)	62 (2.4%)	0.82 (0.56, 1.19) 0.291	236 (9.1%)	232 (9.0%)	1.13 (0.95, 1.36) 0.175
Contralateral breast cancer						
Invasive (total)	15 (0.6%)	25 (1.0%)	0.60 (0.31, 1.14) 0.117	33 (1.3%)	51 (2.0%)	0.64[4] (0.41, 1.00) 0.049

HR = Hazards 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 switching under the ITT principle.

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 Odds ratio and 95% CI for the odds ratio.

Table 5 Disease-free and overall survival by receptor status, nodal status and previous chemotherapy (Modified ITT population)

	2004 analysis – median follow-up 28 months		2008 analysis – median follow-up 62 months[1]	
	HR (95% CI)[2]	***P value***	**HR (95% CI)[2]**	***P value***
Disease-free survival (protocol definition)				
Receptor status positive	0.57 (0.44, 0.75)	0.00003	0.74 (0.62, 0.89)	0.001
Nodal status				
Negative	0.48 (0.30, 0.78)	0.002	0.67 (0.49, 0.93)	0.015
Positive	0.61 (0.44, 0.83)	0.002	0.78 (0.62, 0.97)	0.027
Chemotherapy				
None	0.58 (0.40, 0.84)	0.003	0.71 (0.54, 0.92)	0.010
Received	0.59 (0.41, 0.84)	0.003	0.79 (0.62, 1.01)	0.055
Overall survival				
Nodal status				
Negative	1.36 (0.68, 2.71)	0.385	1.34 (0.99, 1.81)	0.058
Positive	0.61 (0.38, 0.97)	0.035	0.96 (0.75, 1.21)	0.710

HR = Hazards ratio; CI = Confidence Interval

1 Including 60% of eligible patients who switched from placebo to letrozole after the study was unblinded in 2003

2 From Cox regression models

In the updated analysis, as shown in Table 3, there was a significant reduction in the odds of an invasive contralateral breast cancer with Femara compared with placebo, despite 60% of the patients in the placebo arm having switched to Femara. There was no significant difference in overall survival.

There was no difference in safety and efficacy between patients aged <65 versus ≥65 years.

The updated safety profile of Femara did not reveal any new adverse event and was entirely consistent with the profile reported in 2004.

The following adverse events irrespective of causality were reported statistically significantly more often with Femara (n=2567) than with patients who elected not to switch to Femara after the study was unblinded (n=1026) – hot flushes (Femara, 60.9% versus placebo, 51.4%), arthralgia/arthritis (41.5% versus 27.2%), sweating (34.8% versus 29.7%), hypercholesterolemia (23.6% versus 15.3%) and myalgia (17.7% versus 9.4%). Most of these adverse events were observed during the first year of treatment.

For patients who elected to switch to Femara after the study was unblinded, the pattern of general adverse events reported was similar to the pattern during the first two years of treatment in the double-blind study.

Cardiovascular, skeletal and endometrial events were collected with dates of onset and it is possible to report according to the treatment received.

With respect to cardiovascular events, statistically significantly more patients reported overall cardiovascular events with Femara (9.8%) than with placebo (7.0%). Overall cardiovascular events were reported for 6.2% of the patients who elected to switch to Femara. Significantly more patients reported stroke/TIA with Femara (1.5%) than with placebo (0.8%) (Femara after switch, 0.7%); cardiac events (Femara, 2.1% versus placebo, 1.0%) (Femara after switch, 1.4%); and thromboembolic events (Femara, 0.9% versus placebo, 0.3%) (Femara after switch, 0.6%).

Fractures were reported significantly more often with Femara (10.4%) than with placebo (5.8%) (Femara after switch, 7.7%) as was new osteoporosis (Femara, 12.2% versus placebo, 6.4%) (Femara after switch, 5.4%). Irrespective of treatment, patients aged 65 years or older at enrollment experienced more bone fractures and more (new) osteoporosis than younger women.

Updated results (median duration of follow-up was 61 months) from the bone sub-study demonstrated that at 2 years, compared to baseline, patients receiving Femara had a median decrease of 3.8% in hip bone mineral density (BMD) compared to 2.0% in the placebo group (P=0.02). There was no significant difference between treatments in terms of changes in lumbar spine BMD at any time.

Updated results (median follow-up was 62 months) from the lipid sub-study showed no significant difference between the Femara and placebo groups at any time in total cholesterol or in any lipid fraction. In the updated analysis the incidence of cardiovascular events (including cerebrovascular and thromboembolic events) during treatment with Femara versus placebo until switch was 9.8% vs. 7.0%, a statistically significant difference.

First-line treatment of advanced breast cancer:

One well-controlled double-blind trial (Study 025) was conducted comparing letrozole 2.5 mg (n=453) to tamoxifen 20 mg daily (n=454) as first-line therapy in postmenopausal women with locally advanced or metastatic breast cancer. The percentage of patients with hormone receptor positive tumours was 64% in the letrozole group and 67% in the tamoxifen group. Letrozole was superior to tamoxifen in time to progression (primary endpoint) and in overall objective tumour response and time to treatment failure. Time to response and duration of response were the same for both drugs. Specific results are presented in Table 6.

Table 6 Results at a median follow-up of 32 months

Endpoint	**Letrozole 2.5 mg N=453**	**Tamoxifen 20 mg N=454**	**Hazard ratio or odds ratio (95% CI)**
Time to progression (TTP) (median)	9.4 months	6.0 months	0.72 (0.62, 0.83)
Overall objective tumour response (CR + PR)	145 (32%)	95 (21%)	1.78 (1.32, 2.40)
Duration of overall objective tumour response	25 months	23 months	0.74 (0.54, 1.01)
Time to response (median)	14 weeks	14 weeks	0.96 (0.74, 1.25)
Time to treatment failure (TTF) (median)	9.0 months	5.7 months	0.73 (0.64, 0.84)

CR = complete response; PR = partial response
TTP hazard ratios comparing the risk of progression are presented - a hazard ratio of less than 1 favours letrozole, greater than 1 favours tamoxifen.
Response odds ratios for objective tumour response are presented - an odds ratio greater than 1 favours letrozole, less
than 1 favours tamoxifen

Both time to progression and objective response rate were significantly longer/higher for letrozole than for tamoxifen irrespective of receptor status (Table 7).

Table 7 Receptor Status

Endpoint and subgroup	**Letrozole 2.5 mg**	**Tamoxifen 20 mg**	**Hazard ratio or odds ratio (95% CI)**
Receptor positive (ER and/or PgR+)	**N=294**	**N=305**	
Time to progression (TTP)(median)	9.4 months	6.0 months	0.69 (0.58, 0.83)
Response	33%	22%	1.78 (1.2, 2.6)
Receptor Unknown & other*	**N=159**	**N=149**	
Time to progression (TPP)(median)	9.2 months	6.0 months	0.77 (0.60, 0.99)
Response	30%	20%	1.79 (1.1, 3.0)

TTP hazard ratios comparing the risk of progression are presented - a hazard ratio of less than 1 favours letrozole, greater than 1 favours tamoxifen.
Response odds ratios for objective tumour response are presented - an odds ratio greater than 1 favours letrozole, less
than 1 favours tamoxifen.
* 4 patients in the letrozole arm, and none in the tamoxifen arm had one receptor negative and the other unknown, therefore counted as receptor negative.

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 cross-over was virtually completed by 36 months. The median time to cross-over was 17 months (Femara to tamoxifen) and 13 months (tamoxifen to Femara). Femara treatment in the first line therapy of advanced breast cancer patients is associated with an early survival advantage over tamoxifen. The median survival was 34 months for Femara and 30 months for tamoxifen. A significantly greater number of patients were alive on Femara versus tamoxifen throughout the first 24 months of the study (repeated log rank test), see Table 8.

Table 8 Overall survival - Patients alive, died, crossed treatments

	Femara N=458			**Tamoxifen N=458**			**Logrank**
Months	**Alive**	**Deaths**	**Crossed to tamoxifen**	**Alive**	**Deaths**	**Crossed to Femara**	**P-value**
6	426	31	51	406	52	74	0.0167
12	378	79	129	343	114	145	0.0038
18	341	115	185	297	159	179	0.0010
24	286	166	208	263	193	198	0.0246
30	241	209	225	227	227	217	0.0826
36	156	243	233	169	251	224	0.2237
42	70	267	238	85	266	226	0.4820
48	24	277		27	272	228	0.6413
54	6	277		6	276		*0.5303

* Overall Logrank test *P*-value

In patients who did not cross-over to the opposite treatment arm, median survival was 35 months with Femara (N=219, 95% CI 29 to 43 months) vs. 20 months with tamoxifen (N=229, 95% CI 16 to 26 months).

The total duration of endocrine therapy (time to chemotherapy) was significantly longer for Femara (median 16.3 months, 95% CI 15-18 months) than for tamoxifen (median 9.3 months, 95% CI 8 to 12 months) (logrank P=0.0047).

Worsening of Karnofsky Performance Score (KPS) by 20 points or more occurred in significantly fewer patients on Femara (19%) than tamoxifen first-line (25%) (odds ratio 0.69 (0.50-0.94), P=0.0208).

Second-line treatment of advanced breast cancer:

In a well-controlled double-blind clinical trial (Study AR/BC2), 551 postmenopausal women with advanced breast cancer who had relapse or disease progression following antioestrogen (e.g. tamoxifen) therapy were randomised to receive oral daily doses of either Femara 0.5 mg, Femara 2.5 mg or megestrol acetate 160 mg. Some of the patients had also received previous cytotoxic treatment. Patients were either ER positive or unknown status. Data were collected up to 9 months after the last patient was enrolled in the core trial. This was the cut-off date for the primary analysis of response, time to progression, time to failure and safety. For all patients who were still alive at the end of the core trial, whether still on treatment or not, extension data were collected over an additional 6 months (extension trial). The end of the extension trial was the cut-off date for the primary analysis of survival.

At the end of the core trial, the overall objective tumour response (complete and partial response) rate was greatest in patients treated with Femara 2.5 mg (23.6%) compared to patients treated with megestrol acetate (16.4%) and Femara 0.5 mg (12.8%). Comparison of the response rates showed a statistically significant dose-effect in favour of Femara 2.5 mg (P=0.004) with Femara 2.5 mg also statistically superior to megestrol acetate (P=0.04). The median duration of complete and partial response was 18 months for Femara 0.5 mg and for megestrol acetate but was not reached for Femara 2.5 mg. The duration of response was statistically significantly longer with Femara 2.5 mg than with megestrol acetate (P=0.01). The median time to treatment failure was longest for patients on Femara 2.5 mg (155 days) compared to patients on megestrol acetate (118 days) and Femara 0.5 mg (98 days) (P=0.007). The median times to progression were not significantly different. The median times to death (unadjusted analysis) were also not significantly different among the treatment groups in the Kaplan-Meier survival curves with many patients still alive at the last analysis (patients still alive: Femara 0.5 mg (51.6%), Femara 2.5 mg (58.1%), megestrol acetate (50.3%)). Femara gave significantly fewer severe and life threatening side effects, in particular decreased cardiovascular experiences and pulmonary emboli, than megestrol acetate. Other reported drug related adverse events included headache, hot flushes, allergic rash, nausea, hair thinning and oedema (see section 4.8 Adverse effects (Undesirable effects)).

Neoadjuvant treatment of breast cancer:

The safety and efficacy of Femara has not been demonstrated in the neoadjuvant treatment of breast cancer.

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 tmax: 1 hour fasted versus 2 hours fed, and mean Cmax: 129 ± 20.3 nmol/L fasted versus 98.7 ± 18.6 nmol/L 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 14C-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.

Metabolism and Excretion

Metabolic clearance to a pharmacologically inactive carbinol metabolite is the major elimination pathway of letrozole (CLm= 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 14C-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.

The apparent terminal elimination half-life in plasma is about 2 days. After daily administration of 2.5 mg letrozole, 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.

Effect of age or impaired renal / hepatic function on pharmacokinetics:

In the study populations (adults ranging in age from 35 to >80 years), no change in pharmacokinetic parameters was observed with increasing age. In a study involving 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 a similar study involving subjects with varying degrees of hepatic function, the mean AUC values of the volunteers with moderate hepatic impairment (Child-Pugh score 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 subjects with liver cirrhosis and severe hepatic cirrhosis (Child-Pugh score C) to those in healthy subjects (N=8), AUC and t1/2 increased on average by 95 and 187%, respectively, although uncertainty exists about the exact figures because of the wide confidence intervals in the study. Breast cancer patients with this type of severe hepatic impairment are thus expected to be exposed to higher levels of letrozole than patients without severe hepatic dysfunction. The available data do not allow any conclusions to be drawn about patients with predominant hepatocellular damage, for example, those with hepatitis C. If the opinion of the treating doctor is that the risk is acceptable, a patient with severe hepatic impairment may be treated without dose reduction, but close monitoring of possible adverse drug reactions is recommended. In addition, in two well-controlled studies involving 359 patients with advanced breast cancer, no effect of renal impairment (calculated creatinine clearance: 20-50 mL/min) or hepatic dysfunction was found on the letrozole concentration.

5.3 PRECLINICAL SAFETY DATA

Repeat dose toxicity studies of up to 12 months duration were conducted in rats and dogs. No-effect levels were not established for letrozole, but changes observed at the lowest doses used (0.03 mg/kg/day) were related directly to the pharmacological properties of letrozole. Plasma levels of letrozole at the lowest dose in rats and dogs were similar to those expected in post-menopausal women during treatment with letrozole.

At higher doses of letrozole, associated with plasma letrozole concentrations 3 to 100 times greater than those expected in humans, changes were observed in the liver (probably related to the enzyme-inducing properties of letrozole), the pituitary gland, skin, salivary gland, thyroid gland, haematopoietic system, kidneys, adrenal cortex and skeletal system (increased bone fragility). Additional lesions observed at similar doses in studies of longer duration were ocular and cardiac lesions in mice.

In juvenile rats, letrozole treatment beginning on day 7 post partum for 6-12 weeks resulted in skeletal, neuroendocrine and reproductive changes at all doses 0.003-0.3 mg/kg/day; below and similar to the human exposure). Bone growth was decreased in males and increased in females. Bone mineral density (BMD) was decreased in females. Decreased fertility was accompanied by hypertrophy of the hypophysis, testicular changes which

included a degeneration of the seminiferous tubular epithelium and atrophy of the female reproductive tract and ovarian cysts. With the exception of bone size and morphological changes in the testes, all effects were at least partially reversible.

Carcinogenicity

A 104 week carcinogenicity study with oral doses of letrozole at 0.1, 1 or 10 mg/kg/day in rats showed an increased development of ovarian benign gonadal stromal tumours at the highest dose (approximately 400 times human exposure at the maximum recommended clinical dose, based on AUC). Female rats showed a reduced incidence of benign and malignant mammary tumours at all dose levels of letrozole. Female mice treated with oral doses of letrozole at 0.6, 6 or 60 mg/kg/day in a lifetime carcinogenicity study showed an increased incidence of ovarian benign granulosa-theca cell tumours at all dose levels.

Genotoxicity

Letrozole did not show evidence of genotoxicity in *in vitro* assays for gene mutations and *in vitro* and *in vivo* assays for chromosomal damage.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Excipients: colloidal anhydrous silica, microcrystalline cellulose, lactose monohydrate, magnesium stearate, maize starch, sodium starch glycollate, hypromellose, iron oxide yellow, macrogol 8000, purified talc, titanium dioxide.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Tablet containing 2.5mg letrozole in blister packs of 10 and 30 tablets

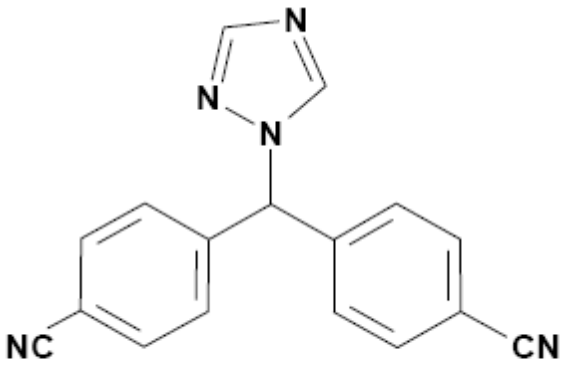
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name of Femara is: 4, 4'-[(1H-1,`2, 4-triazol-1-yl)-methylene] bis-benzonitrile. Its empirical formula is C17H11N5 (MW: 285.3) and its chemical structure is:



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7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Medicine (Schedule 4).

8 SPONSOR

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Section changed	Summary of new information
8	Sponsor address change

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