Drug Regulatory Affairs

FEMARA®

(letrozole)

2.5 mg Film-coated Tablets

Basic Prescribing Information

NOTICE

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.

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1 Trade name of the medicinal product

FEMARA® 2.5 mg film-coated tablets.

2 Qualitative and quantitative composition

Active substance: 4,4'-[(1H-1,2,4-triazol-1-yl)-methylene]bis-benzonitrile (INN/USAN= letrozole) [1].

Each film-coated tablet contains 2.5 mg letrozole [2].

For a full list of excipients, see section 6.1 List of excipients.

3 Pharmaceutical form

Film-coated tablets.

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

Information might differ in some countries.

4 Clinical particulars

4.1 Therapeutic indications

- Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer [61,62].
- Extended adjuvant treatment of early breast cancer in post menopausal women who have received prior standard adjuvant tamoxifen therapy [57,59].
- First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer [52].
- Treatment of advanced breast cancer in women with natural or artificially induced postmenopausal status, who have previously been treated with antioestrogens [3,4].
- Pre-operative therapy in postmenopausal women with localised hormone receptor positive breast cancer, to allow subsequent breast-conserving surgery in women not originally considered candidates for this type of surgery [53]. Subsequent treatment after surgery should be in accordance with standard of care.

4.2 Posology and method of administration

Adult and elderly patients

The recommended dose of Femara® is 2.5 mg once daily [3,4]. In the adjuvant and extended adjuvant setting, treatment with Femara should continue for 5 years or until tumour relapse occurs, whichever comes first [57,59,61,62]. In patients with metastatic disease, treatment with Femara should continue until tumour progression is evident [3,4]. No dose adjustment is required for elderly patients.

Children

Not applicable.

Patients with hepatic and/or renal impairment

No dosage adjustment is required for patients with hepatic impairment [5,50] or renal impairment (creatinine clearance ≥10 mL/min.) [6]. However, patients with severe hepatic impairment (Child-Pugh score C) should be kept under close supervision (see section 5.2 Pharmacokinetic properties).

4.3 Contraindications

- Known hypersensitivity to the active substance or to any of the excipients.
- Premenopausal endocrine status; pregnancy, lactation (see sections 4.6 Pregnancy and lactation and 5.3 Preclinical safety data).

4.4 Special warnings and precautions for use

Renal impairment

Femara has not been investigated in patients with creatinine clearance <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 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 Pharmacokinetic properties).

Bone effects

Osteoporosis and/or bone fractures have been reported with the use of Femara. Therefore monitoring of overall bone health is recommended during treatment (see sections 4.8. Undesirable effects and 5.1 Pharmacodynamic properties) [69,76].

4.5 Interaction with other medicinal products and other forms of interaction

Clinical interaction studies with cimetidine and warfarin indicated that the coadministration of Femara with these drugs does not result in clinically significant drug interactions [8,9].

A review of the clinical trial database indicated no evidence of other clinically relevant interaction with other commonly prescribed drugs.

There is no clinical experience to date on the use of Femara in combination with other anti-cancer agents.

Letrozole inhibits *in vitro* the cytochrome P_{450}-isozymes 2A6, and moderately 2C19. CYP2A6 does not play a major role in drug metabolism. In *in vitro* experiments letrozole, was not able to substantially inhibit the metabolism of diazepam (a substrate of CYP2C19) at concentrations approximately 100-fold higher than those observed in plasma at steady state [45]. Thus, clinically relevant interactions with CYP2C19 are unlikely to occur. However, caution should be used in the concomitant administration of drugs whose disposition is mainly dependent on these isoenzymes and whose therapeutic index is narrow.

4.6 Pregnancy and lactation

Pregnancy

Femara is contraindicated during pregnancy (see sections 4.3 Contraindications and 5.3 Preclinical safety data).

Women of child-bearing potential

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 (see section 5.3 Preclinical safety data) [68].

Lactation

Femara is contraindicated during lactation (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 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 in women who have received prior standard tamoxifen therapy. Approximately one third of the patients treated with Femara in the metastatic and neoadjuvant settings, approximately 75% of the patients in the adjuvant setting (both Femara and tamoxifen arms, at a median treatment duration of 60 months), and approximately 80% of the patients in the extended adjuvant setting (both Femara and placebo arms, at a median treatment duration of 60 months) experienced adverse reactions. Generally, the observed adverse reactions are mainly mild or moderate in nature, and most are associated with oestrogen deprivation [66,74,75].

The most frequently reported adverse reactions in the clinical studies were hot flushes, arthralgia, nausea and fatigue. Many adverse reactions can be attributed to the normal pharmacological consequences of oestrogen deprivation (e.g. hot flushes, alopecia and vaginal bleeding) [3,4,10-14,54,69].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 are ranked under headings of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon ≥1/1000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000), including isolated report.

Infections and infestations Uncommon	Urinary tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	

Uncommon	Tumour pain[6)]
Blood and the lymphatic system disorders	
Uncommon	Leukopenia
Metabolism and nutrition disorders	
Common	Anorexia, appetite increase, hypercholesterolemia [62]
Uncommon	General oedema
Psychiatric disorders	
Common	Depression [62]
Uncommon	Anxiety[1)]
Nervous system disorders	
Common	Headache, dizziness
Uncommon	Somnolence, insomnia, memory impairment, dysaesthesia[2)], taste disturbance, cerebrovascular accident [62]
Eye disorders	
Uncommon	Cataract, eye irritation, blurred vision [60]
Cardiac disorders	
Uncommon	Palpitations, tachycardia
Vascular disorders	
Uncommon	Thrombophlebitis[3)], hypertension, ischemic cardiac events[7,8)] [62]
Rare	Pulmonary embolism, arterial thrombosis, cerebrovascular infarction
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, cough [67]
Gastrointestinal disorders	
Common	Nausea, vomiting, dyspepsia, constipation, diarrhoea
Uncommon	Abdominal pain, stomatitis, dry mouth
Hepatobiliary disorders	
Uncommon	Increased hepatic enzymes [60]
Very rare	Hepatitis [72]
Skin and subcutaneous tissue disorders	
Common	Alopecia, increased sweating, rash[4)]
Uncommon	Pruritus, dry skin, urticaria
Very rare	Angioedema, anaphylactic reaction [71], toxic epidermal necrolysis [73], erythema multiforme [73]
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia [57-59,62,64]
Common	Myalgia, bone pain, osteoporosis [57-59,62,64] bone fractures [57-59,62,64]
Uncommon	Arthritis [57-59,62,64]
Renal and urinary disorders	

Uncommon	Increased urinary frequency
Reproductive system and breast disorders	
Uncommon	Vaginal bleeding, vaginal discharge, vaginal dryness, breast pain
General disorders and administration site conditions	
Very common	Hot flushes
Common	Fatigue[5)], peripheral oedema
Uncommon	Pyrexia, mucosal dryness, thirst
Investigations	
Common	Weight increase
Uncommon	Weight loss

(1) including nervousness, irritability
(2) including paraesthesia, hypoaesthesia
(3) including superficial and deep thrombophlebitis
(4) including erythematous, maculopapular, psoriaform and vesicular rash
(5) including asthenia and malaise
(6) in metastatic/neoadjuvant setting only
(7) 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%) (see section 5.1 Pharmacodynamic properties, Adjuvant treatment) [62,74].
(8) In the extended adjuvant setting, at a median treatment duration of 60 months for letrozole and 37 months for placebo, the following ADRs 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%) (see section 5.1 Pharmacodynamic properties, Extended adjuvant treatment) [75].

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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-steroidal aromatase inhibitor (inhibitor of oestrogen biosynthesis); antineoplastic agent (ATC code L02B G04) [65].

Pharmacodynamic effects

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. It inhibits the aromatase enzyme by competitively binding to the haem of the cytochrome P_{450} subunit of the enzyme, resulting in a reduction of oestrogen biosynthesis in all tissues.

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 to 78% and 78% from baseline, respectively. Maximum suppression is achieved in 48 to 78 hours [15,16].

In postmenopausal patients with advanced breast cancer, daily doses of 0.1 to 5 mg suppress plasma concentration of oestradiol, oestrone, and oestrone sulphate by 75 to 95% from baseline in all patients treated [10,12,17,18]. With doses of 0.5 mg and higher, many values of oestrone and oestrone sulphate are below the limit of detection in the assays, indicating that higher oestrogen suppression is achieved with these doses [3,10,12]. 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-hydroxy-progesterone, and ACTH, or in plasma renin activity among postmenopausal patients treated with a daily dose of letrozole 0.1 to 5 mg [10,12,18]. 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 [12]. 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 [15,16] or in plasma concentrations of androstenedione among postmenopausal patients treated with daily doses of 0.1 to 5 mg [10,12], 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.

Adjuvant treatment

Study BIG 1-98

BIG-98 is a multicenter, double-blind study which randomized over 8,000 postmenopausal women with resected receptor-positive early breast cancer, 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 primary endpoint was disease free survival (DFS), secondary endpoints were overall survival (OS), distant disease free survival (DDFS), systemic disease-free survival (SDFS), invasive contralateral breast cancer, and time to distant metastasis (TDM).

Efficacy results at a median follow-up of 26 months [61]

Data in Tables 2 reflects result 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 in all endpoints except overall survival and 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
Distant disease free survival (secondary)	265	318	0.82 (0.70, 0.97)	0.0204
Overall survival (secondary) - number of deaths (total)	166	192	0.86 (0.70, 1.06)	0.1546
Systemic disease-free survival (secondary)	323	383	0.83 (0.72, 0.97)	0.0172
Contralateral breast cancer (invasive) (secondary)	19	31	0.61 (0.35, 1.08)	0.0910

CI = confidence interval,

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

MAA efficacy results at a median follow-up of 73 months [74]

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 follow-up at the date of the selective crossover (in the tamoxifen arm) are summarized for the MAA (Table 4).

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. Censored analysis of DFS 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) and increased time to distant metastases (HR 0.85; 95% CI 0.72, 1.00). Additionally, overall survival trended towards significance in the ITT analysis. Censored analysis of overall survival 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	509	543	0.85 (0.75, 0.96)	-
Censored analysis of Overall survival	338	338	0.82 (0.70, 0.96)	-

CI = confidence interval,

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

Sequential Treatments Analyses [74]

The Sequential Treatments Analysis (STA) conducted at a median follow up of 48 months addresses the second primary question of the study. The primary analysis for the STA was from switch (or equivalent time-point in monotherapy arms) + 30 days (STA-S) with a two-sided test applied to each pair-wise comparison at the 2.5% level. Additional, exploratory analyses were conducted from randomization (STA-R) at a median follow up of 67 months, with the results for each comparison summarized by hazard ratios and 99% confidence intervals.

At a median follow up of 48 months 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 0.89; 97.5% CI 0.68, 1.15 and [Femara 2 years followed by] tamoxifen 3 years versus Femara beyond 2 years, DFS HR 0.93; 97.5% CI 0.71, 1.22). At a median follow up of 67 months overall, there were no significant differences in any endpoint from randomization in the Sequential Treatments Analysis (e.g. tamoxifen 2 years followed by Femara 3 years versus Femara 5 years, DFS HR 1.10; 99% CI 0.86, 1.41; Femara 2 years followed by tamoxifen 3 years versus Femara 5 years, DFS HR 0.96; 99% CI 0.74, 1.24). 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 [74]

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 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%).

A 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 (2.9% vs. 0.3%), and endometrial proliferate disorders (1.8% vs 0.3%).

Adjuvant Therapy in Early Breast Cancer, Study D2407 [76]

Study D2407 is a phase III, open-label, randomized, multicenter 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

In a multicenter, double-blind, randomized, placebo-controlled study (CFEM345G MA-17), performed in over 5,100 postmenopausal patients with receptor-positive or unknown primary breast cancer 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 [57].

The primary analysis conducted at a median follow-up of around 28 months (25% of the patients being followed-up for up to 38 months) showed that Femara significantly reduced the risk of recurrence by 42% compared with placebo (hazard ratio 0.58; $P=0.00003$). Sensitivity analyses confirmed the robustness of the data. The statistically significant benefit in DFS in

favour of letrozole 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 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. In the updated, final analysis conducted in 2008, 1551 women (60% of those eligible to switch) switched from placebo to Femara at a median 31 months after completion of adjuvant tamoxifen therapy. Median duration of Femara after switch was 40 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 eligible patients in the placebo arm switching to Femara after the study was unblinded. In the Femara arm, median duration of treatment was 60 months; in the placebo arm, median duration of treatment was 37 months. The protocol-specified 4-year DFS rate was identical in the Femara arm for both the 2004 and the 2008 analyses, confirming the stability of the data and robust effectiveness of Femara long-term. In the placebo arm, the increase in 4-year DFS rate at the updated analysis clearly reflects the impact of 60% of the patients having switched to Femara. This switching also accounts for 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 (hazard ratio 1.36; *P*=0.385), in patient with prior chemotherapy or in patients with no prior chemotherapy. See Tables 4 and 5 that summarize the results [57,59,75]:

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 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 (protocol definition)[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) 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) 0.00003	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
Deaths[4]	--	--	--	236[5] (9.1%)	170[6] (6.6%)	0.78

	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**
						(0.64, 0.96)
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[7] (0.41, 1.00) 0.049

HR = Hazards ratio; CI = Confidence Interval

[1] When the study was unblinded in 2003, 1551 patients in the randomized placebo arm (60% of those eligible to switch – i.e. who were disease-free) switched to letrozole at a median 31 months after randomization. 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] 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.

[7] 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 4, 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.

An exploratory analysis censoring follow-up times at the date of switch (if it occurred) showed a significant reduction in the risk of all-cause mortality with Femara compared with placebo (Table 4).

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

The updated safety profile of Femara dd 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 significantly more often with Femara than with placebo – hot flushes (Femara, 61% versus placebo, 51%), arthralgia/arthritis (41% versus 27%), sweating (35% versus 30%), hypercholesterolemia (24% versus 15%) and myalgia (18% versus 9.4%). The majority of these adverse events were observed during the first year of treatment. In the patients in the placebo arm who switched to Femara, a similar pattern of general adverse events was observed. The incidence of osteoporosis during treatment was significantly higher for Femara than for placebo (12.2% versus 6.4%). The incidence of clinical fractures during treatment was significantly higher for Femara than for placebo (10.4% versus 5.8%). In patients who switched to Femara, newly diagnosed osteoporosis during treatement with Femara was reported in 5.4% of patients while fractures were reported in 7.7% of patients. Irrespective of treatment, patients ≥65 years experienced more bone fractures and more osteoporosis.

Updated results (median 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=0.022). There was no significant difference between treatments in changes in lumbar spine BMD at

any time. Updated results (median follow-up was 62 months) from the lipid sub-study showed for any of the lipid measurements no significant difference between the Femara and placebo groups at any time. In the updated analysis, the incidence of cardiovascular events (including cerebrovascular and thromboembolic events) during treatment withr Femara versus placebo until switch was 9.8% vs. 7.8%, a statistically significant difference [57-59,70].

Amongst the pre-printed, check-listed terms during study treatment, the most frequently reported events were: stroke/transient ischemic attack (letrozole, 1.5%; placebo until switch, 0.8%); new or worsening angina (letrozole, 1.4%; placebo until switch, 1.0%); myocardial infarction (letrozole, 1.0%; placebo until switch, 0.7%); thromboembolic events (letrozole, 0.9%; placebo until switch, 0.3%). The reported frequency of thromboembolic events as well as of stroke/transient ischemic attack was significantly higher for Femara than placebo until switch. The interpretation of safety results should consider that there was an unbalance in the median duration of treatment with letrozole (60 months) compared with placebo (37 months) due to the switch from placebo to Femara which occurred in approximately 60% of the patients.

First-line treatment

One well-controlled double-blind trial was conducted comparing Femara 2.5 mg to tamoxifen as first-line therapy in postmenopausal women with locally advanced or metastatic breast cancer [52]. In 907 women, Femara was superior to tamoxifen in time to progression (primary endpoint) and in overall objective response, time to treatment failure and clinical benefit. Specific results are presented in Table 6.

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

	Femara	Tamoxifen	*P*-value
Time to progression (median)	9.4 months	6.0 months	<0.0001
Overall objective tumour response (rate)	32%	21%	0.0002
Duration of overall objective tumour response (median)	25 months	23 months	0.0578
Time to treatment failure (median)	9.1 months	5.7 months	<0.0001
Clinical benefit (rate)	50%	38%	0.0004

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

Table 7 **Receptor status**

	Femara	Tamoxifen	*P*-value
Receptor Status:			
ER and/or PgR+:			
Time to progression (median)	9.4 months	6.0 months	<0.0001
Overall objective tumour response (rate)	33%	22%	0.0019
Unknown/negative:			
Time to progression (median)	9.2 months	6.0 months	0.0402
Overall objective tumour response (rate)	30%	20%	0.0309

ER: oestrogen receptor
PgR: progesterone receptor

The efficacy by dominant disease site is described in Table 8:

Table 8 **Efficacy by dominant disease site**

Dominant disease site	Femara n=453	Tamoxifen n=454	*P*-value
Soft tissue:	**n=113**	**n=115**	
Time to progression (median)	12.1 months	6.4 months	0.0456
Overall objective tumour response	50%	34%	0.0171
Bone:	**n=145**	**n=131**	
Time to progression (median)	9.5 months	6.2 months	0.0262
Overall objective tumour response	23%	15%	0.0891
Viscera:	**n=195**	**n=208**	
Time to progression (median)	8.3 months	4.6 months	0.0005
Overall objective tumour response	28%	17%	0.0095
Liver metastasis:	**n=60**	**n=55**	
Time to progression (median)	3.8 months	3.0 months	0.0232
Overall objective tumour response	10%	11%	0.8735
Rate of overall clinical benefit	28%	16%	0.1292
Overall survival (median) (including crossover)	19 months	12 months	0.0727

Note: “Liver metastasis” is a subset of patients with dominant site of disease in viscera.

Study design allowed patients to crossover 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 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 9 [55].

Table 9 **Overall survival – Patients alive, died, crossed treatments**

	Femara (n=458)			Tamoxifen (n=458)			Logrank
Months	**Alive**	**Deaths**	**Crossed to**	**Alive**	**Deaths**	**Crossed to**	***P*-value**

	Femara (n=458)			Tamoxifen (n=458)			Logrank
			tamoxifen			letrozole	
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 log rank test *P*-value.

The treatment effects analysed by the covariate "prior adjuvant antioestrogen therapy" are detailed in Table 10.

Table 10 Results according to prior adjuvant antioestrogen therapy

	Prior hormone therapy			No prior hormone therapy		
Endpoint	**Femara**	**Tamoxifen**	***P*-value**	**Femara**	**Tamoxifen**	***P*-value**
	n=84	**n=83**		**n=369**	**n=371**	
Time to progression (median)	8.9 months	5.9 months	0.0033	9.5 months	6.0 months	0.0003
Overall objective tumour response	26%	8%	0.0038	33%	24%	0.0039
Clinical benefit	46%	31%	0.0464	51%	40%	0.0026
	n=86	**n=83**		**n=372**	**n=375**	
Overall survival (median) including crossover	28 months	30 months	0.6558	34 months	30 months	0.3756
	n=45	**n=43**		**n=174**	**n=186**	
Survival first-line (patients who did not crossover) (median)	33 months	18 months		33 months	19 months	

In patients who did not crossover 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 to 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 letrozole first-line (19%) than tamoxifen first-line (25%) (odds ratio, *P*=0.0208).

Second-line treatment

Two well-controlled clinical trials were conducted, comparing two letrozole doses (Femara 0.5 mg and 2.5 mg) to megestrol acetate [3,4] and to aminoglutethimide [47-49], respectively,

in postmenopausal women with advanced breast cancer previously treated with antioestrogens.

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

In the second study, Femara 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). The response rate was not significantly different between Femara 2.5 mg and aminoglutethimide (*P*=0.06).

Pre-operative treatment

A double blind trial was conducted in 337 patients randomised to either Femara 2.5 mg for 4 months or tamoxifen for 4 months [53]. There were 55% objective responses in the Femara-treated patients versus 36% for the tamoxifen-treated patients (*P*<0.001) based on clinical assessment. This finding was consistently confirmed by ultrasound (*P*=0.042) and mammography (*P*<0.001), giving the most conservative assessment of response. This response was reflected in a statistically significantly higher number of patients in the Femara group who became suitable for and underwent breast-conserving therapy (45% of patients in the Femara group versus 35% of patients in the tamoxifen group, *P*=0.022).

5.2 Pharmacokinetic properties

Absorption

Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability: 99.9%) [19]. 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/L fasted versus 98.7 ± 18.6 nmol/L fed), but the extent of absorption (AUC) is not changed [20]. The minor effect on the absorption rate is not considered to be of clinical relevance, and therefore letrozole may be taken without regard to meal times.

Distribution

Plasma protein binding of letrozole is approximately 60%, mainly to albumin (55%) [7]. 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 [21]. 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 [19].

Metabolism and elimination

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) [19,22]. The cytochrome P_{450} isoenzymes 3A4 and 2A6 were found to be capable of converting letrozole to this metabolite [22,23]. 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 [21].

The apparent terminal elimination half-life in plasma is about 2 days [19]. After daily administration of 2.5 mg, steady-state levels are reached within 2 to 6 weeks [11]. 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 [3,10,11].

Age had no effect on the pharmacokinetics of letrozole [3].

Special populations

In a study involving volunteers with varying degrees of renal function (24-hour creatinine clearance 9 to 116 mL/min), no effect on the pharmacokinetics of letrozole was found after a single dose of 2.5 mg [6]. In a similar study involving subjects with varying degrees of hepatic function [5], 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 [19,20,21]. In a study comparing the pharmacokinetics of letrozole after a single oral dose in eight subjects with liver cirrhosis and severe hepatic impairment (Child-Pugh score C) to those in healthy volunteers (n=8), AUC and $t_{1/2}$ increased by 95 and 187%, respectively [50]. Breast-cancer patients with severe hepatic impairment are thus expected to be exposed to higher levels of letrozole than patients without severe hepatic dysfunction. However, since in patients dosed at 5 or 10 mg/day [12,51] no increase in toxicity was observed, a dose reduction in patients with severe hepatic impairment appears not to be warranted, although such patients should be kept under close supervision. In addition, in two well-controlled studies involving 359 patients with advanced breast cancer, no effect of renal impairment (calculated creatinine clearance: 20 to 50 mL/min) or hepatic dysfunction was found on the letrozole concentration [3,47].

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 to up to 2,000 mg/kg [24-26]. In dogs, letrozole caused signs of moderate toxicity at 100 mg/kg [27].

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 [28-34].

The pharmacological effects of letrozole resulted in skeletal, neuroendocrine and reproductive findings in a juvenile rat study. Bone growth and maturation were decreased from the lowest dose (0.003 mg/kg/day) in males and increased from the lowest dose (0.003 mg/kg) in

females. Bone mineral density (BMD) was also decreased at that dose in females. In the same study, decreased fertility at all doses 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. With the exception of bone size in females and morphological changes in the testes, all effects were at least partially reversible [77].

Both *in vitro* and *in vivo* investigations on letrozole's mutagenic potential revealed no indications of any genotoxicity [35-40].

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 [41].

Oral administration of letrozole to gravid rats resulted in a slight increase in the incidence of fetal malformation among the animals treated. However, 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 (see recommendations in sections 4.3 Contraindications and 4.6 Pregnancy and lactation).

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

Colloidal anhydrous silica, microcristalline cellulose, lactose monohydrate, magnesium stearate, maize starch, sodium starch glycollate, hydroxypropyl methylcellulose, polyethylene glycol 8000, talc, titanium dioxide (E 171), iron oxide yellow (E 172) [2].

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years [46,56].

Information might differ in some countries.

6.4 Special precautions for storage

Do not store above 30°C and do protect from moisture [46,56].

Information might differ in some countries.

Femara should be kept out of the reach and sight of children.

6.5 Nature and contents of container

PVC/PE/PVDC blister packs.

6.6 Instructions for use/handling

No specific instructions for use/handling.

This is a non-referenced document.