

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FEMAPLEX 2.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5 mg letrozole.

Each tablet contains 61.5 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Letrozole are yellow round, biconvex film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.
- Extended adjuvant treatment of hormone-dependent early breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy for 5 years.
- First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer.
- Advanced breast cancer in women with natural or artificially induced postmenopausal status after relapse or disease progression, who have previously been treated with anti-oestrogens.

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

4.2. Posology and method of administration

Adult and elderly patients

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

In the adjuvant setting, it is recommended to treat for 5 years or until tumour relapse occurs.

In the adjuvant setting, clinical experience is available for 2 years (median duration of treatment was 25 months).

In the extended adjuvant setting, clinical experience is available for 4 years (median duration of treatment).

In patients with advanced or metastatic disease, treatment with Letrozole should continue until tumour progression is evident.

Children

Not applicable.

Patients with hepatic and/or renal impairment

No dosage adjustment is required for patients with renal insufficiency with creatinine clearance greater than 30 ml/min.

Insufficient data are available in cases of renal insufficiency with creatinine clearance lower than 30 ml/min or in patients with severe hepatic insufficiency (see sections 4.4 and 5.2).

4.3 Contraindications

- 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

In patients whose postmenopausal status seems unclear, LH, FSH and/or oestradiol levels must be assessed before initiating treatment in order to clearly establish menopausal status.

Renal Impairment

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

Hepatic Impairment

Letrozole has only been studied in a limited number of non-metastatic patients with varying degrees of hepatic function: mild to moderate, and severe hepatic insufficiency. In non-cancer male volunteers with severe hepatic impairment (liver cirrhosis and Child-Pugh score C), systemic exposure and terminal half-life were increased 2-3-fold compared to healthy volunteers. Thus, letrozole should be administered with caution and after careful consideration of the potential risk/benefit to such patients (see section 5.2 Pharmacokinetic properties).

Bone Effects

Letrozole is a potent oestrogen-lowering agent. In the adjuvant and extended adjuvant setting the median follow-up duration of 30 and 49 months respectively is insufficient to fully assess fracture risk associated with long term use of letrozole. Women with a history of osteoporosis and/or fractures or who are at increased risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry prior to the commencement of adjuvant and extended adjuvant treatment and be monitored for development of osteoporosis during and following treatment with letrozole. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored (see section 4.8 Undesirable effects).

As the tablets contain lactose, Letrozole is not recommended for patients with rare hereditary problems of galactose intolerance, of severe lactase deficiency or of glucose-galactose malabsorption.

4.5. Interactions with other medicinal products and other forms of interaction

Clinical interaction studies with cimetidine and warfarin indicated that the coadministration of letrozole with these drugs does not result in clinically significant drug interactions.

Additionally, a review of the clinical trial database indicated no evidence of clinically relevant interactions with other commonly prescribed drugs.

There is no clinical experience to date on the use of letrozole in combination with other anticancer agents.

In vitro, letrozole inhibits the cytochrome P450 isoenzymes 2A6 and, moderately, 2C19. Thus, 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

Women of perimenopausal status or child-bearing potential

The physician needs to discuss the necessity of a pregnancy test before initiating Letrozole and of adequate contraception with women who have the potential to become pregnant (i.e. women who are perimenopausal or who recently became postmenopausal) until their postmenopausal status is fully established (see sections 4.4 Special warnings and precautions for use and 5.3 Preclinical safety data).

Pregnancy

Letrozole is contraindicated during pregnancy (see section 4.3 Contraindications and 5.3 Preclinical safety data).

Lactation

Letrozole is contraindicated during lactation (see section 4.3 Contraindications).

4.7. Effects on the ability to drive and operate machinery

Since fatigue and dizziness have been observed with the use of Letrozole and somnolence has been reported uncommonly, caution is advised when driving or using machines.

4.8. Undesirable effects

Letrozole was generally well tolerated across all studies as first-line and second-line treatment for advanced breast cancer and as adjuvant treatment of early breast cancer. Up to approximately one third of the patients treated with letrozole in the metastatic setting, up to approximately 70-75% of the patients in the adjuvant setting (both letrozole and tamoxifen arms), and up to approximately 40 % of the patients treated in the extended adjuvant setting (both letrozole and placebo arms) experienced adverse reactions. Generally, the observed adverse reactions are mainly mild or moderate in nature. Most adverse reactions can be

attributed to normal pharmacological consequences of oestrogen deprivation (e.g. hot flushes).

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).

After standard adjuvant tamoxifen, based on median follow-up of 28 months, the following adverse events irrespective of causality were reported significantly more often with letrozole than with placebo- hot flushes (50.7% vs. 44.3%), arthralgia/arthritis (28.5% vs. 23.2%) and myalgia (10.2% vs. 7.0%). The majority of these adverse events were observed during the first year of treatment. There was a higher but non significant incidence of osteoporosis and bone fractures in patients who received letrozole than in patients who received placebo (7.5% vs. 6.3% and 6.7% vs. 5.9%, respectively).

In an updated analysis in the extended adjuvant setting conducted at a median treatment duration of 47 months for letrozole and 28 months for placebo, the following adverse events irrespective of causality were reported significantly more often with letrozole than with placebo – hot flushes (60.3% vs. 52.6%), arthralgia/arthritis (37.9% vs. 26.8%) and myalgia (15.8% vs. 8.9%). The majority of these adverse events were observed during the first year of treatment. In the patients in placebo arm who switched to letrozole a similar pattern of general events was observed. There was a higher incidence of osteoporosis and bone fractures, any time after randomisation, in patients who received letrozole than in patients who received placebo (12.3% vs. 7.4% and 10.9% vs. 7.2%, respectively). In patients who switched to letrozole, newly diagnosed osteoporosis, any time after switching, was reported in 3.6% of patients while fracture were reported in 5.1% of patients any time after switching.

In the adjuvant setting, irrespective of causality, the following adverse events occurred any time after randomization in the letrozole and tamoxifen groups respectively: thromboembolic events (1.5% vs. 3.2%, $P<0.001$), angina pectoris (0.8% vs. 0.8%), myocardial infarction (0.7% vs. 0.4%) and cardiac failure (0.9% vs. 0.4%, $P=0.006$).

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

Table 1

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: very common $\geq 10\%$, common $\geq 1\%$ to $< 10\%$, uncommon $\geq 0.1\%$ to $< 1\%$, rare $\geq 0.01\%$ to $< 0.1\%$, very rare $< 0.01\%$, including isolated reports.

Infections and infestations

Uncommon: Urinary tract infection

Neoplasms, benign, malignant and unspecified (including cysts and polyps)

Uncommon: Tumour pain (not applicable in the adjuvant and extended adjuvant setting)

Blood and the lymphatic system disorders

Uncommon: Leukopenia

Metabolism and nutrition disorders

Common: Anorexia, appetite increase, hypercholesterolaemia

Uncommon: General oedema

Psychiatric disorders

Common: Depression

Uncommon: Anxiety including nervousness, irritability

Nervous system disorders

Common: Headache, dizziness

Uncommon: Somnolence, insomnia, memory impairment, dysaesthesia including paresthesia, hypoesthesia, taste disturbance, cerebrovascular accident

Eye disorders

Uncommon: Cataract, eye irritation, blurred vision

Cardiac disorders

Uncommon: Palpitations, tachycardia

Vascular disorders

Uncommon: Thrombophlebitis including superficial and deep thrombophlebitis, hypertension, ischemic cardiac events

Rare: Pulmonary embolism, arterial thrombosis, cerebrovascular infarction

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea, cough

Gastrointestinal disorders

Common: Nausea, vomiting, dyspepsia, constipation, diarrhoea

Uncommon: Abdominal pain, stomatitis, dry mouth

Hepatobiliary disorders

Uncommon: Increased hepatic enzymes

Not known: Hepatitis

Skin and subcutaneous tissue disorders

Very common: Increased sweating

Common: Alopecia, rash including erythematous, maculopapular, psoriaform, and vesicular rash

Uncommon: Pruritus, dry skin, urticaria

Not known: Anaphylactic reaction, angioedema, toxic epidermal necrolysis, erythema multiforme

Musculoskeletal and connective tissue disorders

Very common: Arthralgia

Common: Myalgia, bone pain, osteoporosis, bone fractures

Uncommon: Arthritis

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, fatigue including asthenia

Common: Malaise, peripheral oedema

Uncommon: Pyrexia, mucosal dryness, thirst

Investigations

Common: Weight increase

Uncommon: Weight loss

4.9. Overdose

Isolated cases of overdosage with letrozole 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: Enzyme inhibitor. Non-steroidal aromatase inhibitor (inhibitor of oestrogen biosynthesis); antineoplastic agent, ATC code: L02B G04.

Pharmacodynamic effects

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

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

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

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 75-95% from baseline in all patients treated. 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. Oestrogen suppression was maintained throughout treatment in all these patients.

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

No changes were noted in plasma concentrations of androgens (androstenedione and testosterone) among healthy postmenopausal women after 0.1, 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 are not affected by letrozole in patients, nor is thyroid function as evaluated by TSH, T4, and T3 uptake test.

Adjuvant treatment

A multicenter, double-blind study randomized over 8000 postmenopausal women with resected receptor-positive early breast cancer, to one of the following option:

Option 1:

- A. tamoxifen for 5 years
- B. letrozole for 5 years
- C. tamoxifen for 2 years followed by letrozole for 3 years
- D. letrozole for 2 years followed by tamoxifen for 3 years

Option 2:

- A. tamoxifen for 5 years
- B. letrozole for 5 years

Data in Table 2 reflect results based on data from the monotherapy arms in each randomization option and data from the two switching arms up to 30 days after the date of switch. The analysis of monotherapy vs sequencing of endocrine treatments will be conducted when the necessary number of events has been achieved.

Patients have been followed for a median of 26 months, 76% of the patients for more than 2 years, and 16% (1252 patients) for 5 years or longer.

The primary endpoint of the trial was disease-free survival (DFS) which was assessed as the time from randomization to the earliest event of loco-regional or distant recurrence (metastases) of the primary disease, development of invasive contralateral breast cancer, appearance of a second non-breast primary tumor or death from any cause without a prior cancer event. Letrozole reduced the risk of recurrence by 19% compared with tamoxifen (hazard ratio 0.81; P=0.003). The 5-year DFS rates were 84.0% for letrozole and 81.4% for

tamoxifen. The improvement in DFS with letrozole is seen as early as 12 months and is maintained beyond 5 years. Letrozole also significantly reduced the risk of recurrence compared with tamoxifen whether prior adjuvant chemotherapy was given (hazard ratio 0.72 ; P=0.018) or not (hazard ratio 0.84 ; P=0.044).

For the secondary endpoint overall survival a total of 358 deaths were reported (166 on letrozole and 192 on tamoxifen). There was no significant difference between treatments in overall survival (hazard ratio 0.86; P=0.15). Distant disease-free survival (distant metastases), a surrogate for overall survival, differed significantly overall (hazard ratio 0.73; P=0.001) and in pre-specified stratification subsets. Letrozole significantly reduced the risk of systemic failure by 17% compared with tamoxifen (hazard ratio 0.83; P=0.02)

However, although in favour of letrozole non significant difference was obtained in the contralateral breast cancer (hazard ratio 0.61; P=0.09). An exploratory analysis of DFS by nodal status showed that letrozole was significantly superior to tamoxifen in reducing the risk of recurrence in patients with node positive disease (HR 0.71; 95% CI 0.59, 0.85; P=0.0002) while no significant difference between treatments was apparent in patients with node negative disease (HR 0.98; 95% CI 0.77, 1.25; P=0.89). This reduced benefit in node negative patients was confirmed by an exploratory interaction analysis (p=0.03).”

Patients receiving letrozole, compared to tamoxifen, had fewer second malignancies (1.9% vs 2.4%). Particularly the incidence of endometrial cancer was lower with letrozole compared to tamoxifen (0.2% vs 0.4%).

See Tables 2 and 3 that summarize the results. The analyses summarized in Table 4 omit the 2 sequential arms from randomization option 1, i.e. take account only of the monotherapy arms:

Table 2 Disease-free and overall survival (ITT population)

	Letrozole N=4003	Tamoxifen N=4007	Hazard (95 % CI)	Ratio	P-Value¹
Disease-free survival (primary)					
- events (protocol definition, total)	351	428	0.81 (0.70, 0.93)		0.0030
Distant disease-free survival (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 (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

Table 3 Disease-free and overall survival by nodal status and prior adjuvant chemotherapy (ITT population)

	Hazard Ratio, 95% CI for hazard ratio	P-Value¹
Disease-free survival		
Nodal status		
- Positive	0.71 (0.59, 0.85)	0.0002
- Negative	0.98 (0.77, 1.25)	0.8875
Prior adjuvant chemotherapy		
- Yes	0.72 (0.55, 0.95)	0.0178

	Hazard Ratio, 95% CI for hazard ratio	P-Value ¹
- No	0.84 (0.71, 1.00)	0.0435
Overall survival		
Nodal status		
- Positive	0.81 (0.63, 1.05)	0.1127
- Negative	0.88 (0.59, 1.30)	0.5070
Prior adjuvant chemotherapy		
- Yes	0.76 (0.51, 1.14)	0.1848
- No	0.90 (0.71, 1.15)	0.3951
Distant disease-free survival		
Nodal status		
- Positive	0.67 (0.54, 0.84)	0.0005
- Negative	0.90 (0.60, 1.34)	0.5973
Prior adjuvant chemotherapy		
- Yes	0.69 (0.50, 0.95)	0.0242
- No	0.75 (0.60, 0.95)	0.0184

CI = confidence interval

¹ Cox model significance level

Table 4 Primary Core Analysis: Efficacy endpoints according to randomization option monotherapy arms (ITT population)

Endpoint	Option	Statistic	Letrozole	Tamoxifen
DFS (Primary, definition)	1	Events / n	100 / 1546	137 / 1548
		HR (95% CI), <i>P</i>	0.73 (0.56, 0.94), 0.0159	
	2	Events / n	177 / 917	202 / 911
		HR (95% CI), <i>P</i>	0.85 (0.69, 1.04), 0.1128	
	Overall	Events / n	277 / 2463	339 / 2459
		HR (95% CI), <i>P</i>	0.80 (0.68, 0.94), 0.0061	
DFS (excluding malignancies)	1	Events / n	80 / 1546	110 / 1548
		HR (95% CI), <i>P</i>	0.73 (0.54, 0.97), 0.0285	
	2	Events / n	159 / 917	187 / 911
		HR (95% CI), <i>P</i>	0.82 (0.67, 1.02), 0.0753	
	Overall	Events / n	239 / 2463	297 / 2459
		HR (95% CI), <i>P</i>	0.79 (0.66, 0.93), 0.0063	
Distant DFS (Secondary)	1	Events / n	57 / 1546	72 / 1548
		HR (95% CI), <i>P</i>	0.79 (0.56, 1.12), 0.1913	
	2	Events / n	98 / 917	124 / 911
		HR (95% CI), <i>P</i>	0.77 (0.59, 1.00), 0.0532	
	Overall	Events / n	155 / 2463	196 / 2459
		HR (95% CI), <i>P</i>	0.78 (0.63, 0.96), 0.0195	

Endpoint	Option	Statistic	Letrozole	Tamoxifen
Overall survival (Secondary)	1	Events / n	41 / 1546	48 / 1548
		HR (95% CI), <i>P</i>	0.86 (0.56, 1.30), 0.4617	
	2	Events / n	98 / 917	116 / 911
		HR (95% CI), <i>P</i>	0.84 (0.64, 1.10), 0.1907	
	Overall	Events / n	139 / 2463	164 / 2459
		HR (95% CI), <i>P</i>	0.84 (0.67, 1.06), 0.1340	

P-value given is based on logrank test, stratified by adjuvant chemotherapy for each randomization option, and by randomization option and adjuvant chemotherapy for overall analysis

The median duration of treatment (safety population) 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 for both letrozole and tamoxifen.

Adverse events suspected of being related to study drug were reported for 78% of the patients treated with letrozole compared with 73% of those treated with tamoxifen. The most common adverse events experienced with letrozole were hot flushes, night sweats, arthralgia, weight increase, and nausea. Of these, only arthralgia occurred significantly more often with letrozole than with tamoxifen (20% vs 13% for tamoxifen). Letrozole treatment was associated with a higher risk of osteoporosis (2.2% vs 1.2% with tamoxifen). Overall, irrespective of causality, cardiovascular/cerebrovascular events were reported any time after randomization for similar proportions of patients in both treatment arms (10.8% for letrozole, 12.2% for tamoxifen). Amongst these, thromboembolic events were reported significantly less often with letrozole (1.5%) than with tamoxifen (3.2%) ($P < 0.001$), while cardiac failure was reported significantly more often with letrozole (0.9%) than with tamoxifen (0.4%) ($P = 0.006$). Amongst patients who had baseline values of total serum cholesterol within the normal range, increases in total serum cholesterol higher than 1.5 times the ULN were observed in 5.4% of the patients in the letrozole arm, compared with 1.1% in the tamoxifen arm.

Extended adjuvant treatment

In a multicentre, double-blind, randomised, placebo-controlled study, 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 letrozole or placebo.

The primary analysis conducted at a median follow-up of around 28 months (25% patients of the patients being followed for at least 38 months) showed that letrozole reduced the risk of recurrence by 42% compared with placebo (hazard ratio 0.58 ; $P = 0.00003$). 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 ; $P = 0.002$.

For the secondary endpoint overall survival (OS) a total of 113 deaths were reported (51 letrozole, 62 placebo). Overall, there was no significant difference between treatments in OS (hazard ratio 0.82; $P = 0.29$).

Afterwards the study continued in an unblinded fashion and patients in the placebo arm could switch to letrozole , if they wished to do so. After the study unblinding, over 60% of the patients in the placebo arm eligible to switch opted to switch to letrozole (i.e., late extended adjuvant population). Patients who switched to letrozole from placebo had been off adjuvant tamoxifen for a median 31 months (range 14 to 79 months).

Updated intent-to-treat analyses were conducted at a median follow-up of 49 months. In the letrozole arm at least 30% of the patients had completed 5 years and 59% had completed at least 4 years of follow-up. In the updated analysis of DFS, letrozole significantly reduced the risk of breast cancer recurrence compared

with placebo (hazard ratio 0.68 ; 95% CI 0.55,0.83 ; $P=0.0001$). letrozole also significantly reduced the odds of a new invasive contralateral cancer by 41% compared with placebo (odds ratio 0.59 ; 95% CI 0.36, 0.96 ; $P=0.03$). There was no significant difference in distant disease-free survival or overall survival.

Updated results (median duration of follow-up was 40 months) from the bone mineral density (BMD) substudy (226 patients enrolled) demonstrated that, at 2 years, compared to baseline, patients receiving letrozole were associated with greater decreases in BMD in the total hip (median decrease of 3.8% in hip BMD compared to a median decrease of 2.0% in the placebo group ($P=0.012$, adjusted for bisphosphonate use, $P=0.018$). Patients receiving letrozole were associated with a greater decrease in lumbar spine BMD although not significantly different.

Concomitant calcium and vitamin D supplementation was mandatory in the BMD substudy.

Updated results (median duration of follow-up was 50 months) from the Lipid substudy (347 patients enrolled) show no significant differences between the letrozole and placebo arms in total cholesterol or in any lipid fraction.

In the updated analysis of the core study 11.1% of patients in the letrozole arm reported cardiovascular adverse events during treatment compared with 8.6% in the placebo arm until switch. These events included myocardial infarction (letrozole 1.3%, placebo 0.9%); angina requiring surgical intervention (letrozole 1.0%, placebo 0.8%), new or worsening angina (letrozole 1.7% vs placebo 1.2%), thromboembolic events (letrozole 1.0%, placebo 0.6%) and cerebrovascular accident (letrozole 1.7% vs placebo 1.3%).

No significant differences were observed on global physical and mental summary scores, suggesting that overall, letrozole did not worsen quality of life relative to placebo. Treatment differences in favour of placebo were observed in patients` assessments with particularly the measures of physical functioning, bodily pain, vitality, sexual and vasomotor items. Although statistically significant these differences were not considered clinically relevant.

First-line treatment:

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

The results are summarized in Table 5:

Table 5		Results at a median follow-up of 32 months	
Variable	Statistic	letrozole n=453	Tamoxifen n=454
Time to progression	Median	9.4 months	6.0 months

Variable	Statistic	letrozole n=453	Tamoxifen n=454
Objective response rate (ORR)	(95% CI for median)	(8.9, 11.6 months)	(5.4, 6.3 months)
	Hazard ratio (HR)	0.72	
	(95% CI for HR)	(0.62, 0.83)	
	<i>P</i>	<0.0001	
	CR+PR	145 (32%)	95 (21%)
Overall clinical benefit rate	(95% CI for rate)	(28, 36%)	(17, 25%)
	Odds ratio	1.78	
	(95% CI for odds ratio)	(1.32, 2.40)	
	<i>P</i>	0.0002	
	CR+PR+NC \geq 24 weeks	226 (50%)	173 (38%)
Time to treatment failure	Odds ratio	1.62	
	(95% CI for odds ratio)	(1.24, 2.11)	
	<i>P</i>	0.0004	
	Median	9.1 months	5.7 months
	(95% for median)	(8.6, 9.7 months)	(3.7, 6.1 months)
	Hazard ratio	0.73	
	(95% CI for HR)	(0.64, 0.84)	
	<i>P</i>	<0.0001	

Time to progression was significantly longer, and response rate was significantly higher for letrozole than for tamoxifen in patients with tumours of unknown receptor status as well as with positive receptor status. Similarly, time to progression was significantly longer, and response rate significantly higher for letrozole irrespective of whether adjuvant anti-oestrogen therapy had been given or not. Time to progression was significantly longer for letrozole irrespective of dominant site of disease. Median time to progression was almost twice as long for letrozole in patients with soft tissue disease only (median 12.1 months for letrozole, 6.4 months for tamoxifen), and in patients with visceral metastases (median 8.3 months for letrozole, 4.6 months for tamoxifen). Response rate was significantly higher for letrozole in patients with soft tissue disease only (50% vs 34% for letrozole and tamoxifen respectively), and for patients with visceral metastases (28% letrozole vs 17% tamoxifen).

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

letrozole treatment in the first-line therapy of advanced breast cancer resulted in a median overall survival of 34 months compared with 30 months for tamoxifen (logrank test $P=0.53$, not significant). Better survival was associated with letrozole up to at least 24 months. The survival rate at 24 months was 64% for the letrozole treatment group versus 58% for the tamoxifen treatment group. The absence of an advantage for letrozole on overall survival could be explained by the crossover design of the study.

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

Second-line treatment:

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

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

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

letrozole

5.2. Pharmacokinetic properties

Absorption

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

Distribution

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

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). The cytochrome P450 isoenzymes 3A4 and 2A6 were found to be capable of converting letrozole to this metabolite. Formation of minor unidentified metabolites and direct renal and faecal excretion play only a minor role in the overall elimination of letrozole. Within 2 weeks after administration of 2.5 mg ^{14}C -labelled letrozole to healthy postmenopausal volunteers, $88.2 \pm 7.6\%$ of the radioactivity was recovered in urine and $3.8 \pm 0.9\%$ in faeces. At least 75% of the radioactivity recovered in urine up to 216 hours ($84.7 \pm 7.8\%$ of the dose) was attributed to a 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 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.

Age had no effect on the pharmacokinetics of letrozole.

Special populations

In a study involving 19 volunteers with varying degrees of renal function (24-hour creatinine clearance 9-116 ml/min) no effect on the pharmacokinetics of letrozole was found after a single dose of 2.5 mg. In 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 male 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. Thus letrozole should be administered with caution and after consideration of the potential risk/benefit to such patients.

5.3. Preclinical Safety Data

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

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

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

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

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

Oral administration of letrozole to gravid rats resulted in a slight increase in the incidence of foetal 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 recommendation 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

Lactose monohydrate
Maize Starch
Microcrystalline Cellulose
Sodium Starch glycolate (type A)
Silica
Colloidal anhydrous Magnesium Stearate.

The tablets are coated with:

Macrogol
Hypromellose
Talc
Titanium dioxide (E171)
Yellow Iron Oxide (E172)
Red Iron Oxide (E172).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions

6.5. Nature and contents of container

PVC/PE/PVDC-Aluminium blister packs
The tablets are packed in blisters of 30 and 100 tablets.

Not all pack sizes will be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST REGISTRATION/RENEWAL OF REGISTRATION

10. DATE OF REVISION OF THE TEXT