

Annex III

Summary of product characteristics, labelling and package leaflet

Note: This SPC, labelling and packages leaflet is the version valid at the time of Commission decision.

After the Commission decision the Member State competent authorities, in liaison with the reference Member State, will update the product information as required. Therefore, this SPC, labelling and package leaflet may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

{Invented name} and associated names (see Annex I) strength pharmaceutical form
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

Posology

Adult and elderly patients

The recommended dose of {Invented Name} is 2.5 mg once daily. No dose adjustment is required for elderly patients.

In patients with advanced or metastatic breast cancer, treatment with {Invented Name} should continue until tumour progression is evident.

In the adjuvant and extended adjuvant setting, treatment with {Invented Name} should continue for 5 years or until tumour relapse occurs, whichever is first.

In the adjuvant setting a sequential treatment schedule (letrozole 2 years followed by tamoxifen 3 years) could also be considered (see sections 4.4 and 5.1).

In the neoadjuvant setting, treatment with {Invented Name} could be continued for 4 to 8 months in order to establish optimal tumour reduction. If the response is not adequate, treatment with {Invented Name} should be discontinued and surgery scheduled and/or further treatment options discussed with the patient.

Paediatric population

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

Renal impairment

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

Hepatic impairment

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

Method of administration

{Invented Name} should be taken orally and can be taken with or without food.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Menopausal status

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

Renal impairment

{Invented Name} 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 {Invented Name}.

Hepatic impairment

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

Bone effects

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

Other warnings

Co-administration of {Invented Name} with tamoxifen, other anti-oestrogens or oestrogen-containing therapies should be avoided as these substances may diminish the pharmacological action of letrozole (see

section 4.5).

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

4.6 Fertility, pregnancy and lactation

Women of perimenopausal status or child-bearing potential

{Invented Name} should only be used in women with a clearly established postmenopausal status (see section 4.4). As there are reports of women regaining ovarian function during treatment with {Invented Name} despite a clear postmenopausal status at start of therapy, the physician needs to discuss adequate contraception when necessary.

Pregnancy

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

{Invented Name} is contraindicated during pregnancy (see sections 4.3 and 5.3).

Breast-feeding

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

{Invented Name} is contraindicated during breast-feeding (see section 4.3).

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The frequencies of adverse reactions for {Invented Name} are mainly based on data collected from clinical trials.

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

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

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

Tabulated listing of adverse reactions

The frequencies of adverse reactions for {Invented Name} are mainly based on data collected from clinical trials.

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

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 $< 0.01\%$, not known (cannot be estimated from the available data).

Infections and infestations	
Uncommon:	Urinary tract infection
Neoplasms, benign, malignant and unspecified (including cysts and polyps)	
Uncommon:	Tumour pain ¹
Blood and the lymphatic system disorders	
Uncommon:	Leukopenia
Immune system disorders	
Not known:	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
Uncommon:	Somnolence, insomnia, memory impairment, dysaesthesia (including paraesthesia, hypoaesthesia), taste disturbance, cerebrovascular accident
Eye disorders	
Uncommon	Cataract, eye irritation, blurred vision
Cardiac disorders	
Uncommon:	Palpitations ¹ , tachycardia, ischaemic cardiac events(including new or worsening angina, angina requiring surgery, myocardial infarction and myocardial ischaemia)

Vascular disorders	
Very common:	Hot flushes
Common:	Hypertension
Uncommon:	Thrombophlebitis (including superficial and deep vein thrombophlebitis)
Rare:	Pulmonary embolism, arterial thrombosis, cerebrovascular infarction
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Dyspnoea, cough
Gastrointestinal disorders	
Common:	Nausea, dyspepsia ¹ , constipation, abdominal pain, diarrhoea, vomiting
Uncommon:	Dry mouth, stomatitis ¹
Hepatobiliary disorders	
Uncommon:	Increased hepatic enzymes
Not known:	Hepatitis
Skin and subcutaneous tissue disorders	
Very common:	Increased sweating
Common:	Alopecia, rash (including erythematous, maculopapular, psoriaform, and vesicular rash), dry skin
Uncommon:	Pruritus, urticaria
Not known:	Angioedema, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia
Common:	Myalgia, bone pain ¹ , osteoporosis, bone fractures
Uncommon:	Arthritis
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 asthenia, malaise)
Common:	Peripheral oedema
Uncommon:	General oedema, mucosal dryness, thirst, pyrexia
Investigations	
Common:	Weight increase
Uncommon:	Weight loss

¹ Adverse drug reactions reported only in the metastatic setting

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

Table 2 Adjuvant {Invented Name} monotherapy versus tamoxifen monotherapy – adverse events with significant differences

	{Invented Name}, incidence rate	Tamoxifen, incidence rate
Bone fracture	10.1% (13.8%)	7.1% (10.5%)
Osteoporosis	5.1% (5.1%)	2.7% (2.7%)
Thromboembolic events	2.1% (2.9%)	3.6% (4.5%)
Myocardial infarction	1.0% (1.5%)	0.5% (1.0%)
Endometrial hyperplasia / endometrial cancer	0.2% (0.4%)	2.3% (2.9%)

Note: Median duration of treatment 60 months. Reporting period includes treatment period plus 30 days after stopping treatment.
Percentages in parentheses indicate event frequencies any time after randomisation, including post study treatment period. Median follow-up was 73 months.

Table 3 Sequential treatment versus {Invented Name} monotherapy – adverse events with significant differences

	{Invented Name} monotherapy	{Invented Name}->tamoxifen	Tamoxifen->{Invented Name}
Bone fractures	9.9%	7.6%*	9.6%
Endometrial proliferative disorders	0.7%	3.4%**	1.7%**
Hypercholesterolaemia	52.5%	44.2%*	40.8%*
Hot flushes	37.7%	41.7%**	43.9%**
Vaginal bleeding	6.3%	9.6%**	12.7%**

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

Description of selected adverse reactions

Cardiac adverse reactions

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

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

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

Skeletal adverse reactions

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

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

4.9 Overdose

Isolated cases of overdose with {Invented Name} have been reported.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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 mg, 0.5 mg, and 2.5 mg letrozole suppress serum oestrone and oestradiol by 75%, 78% and 78% from baseline, respectively. Maximum suppression is achieved in 48-78 hours.

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

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

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

Adjuvant treatment

Study BIG 1-98

BIG 1-98 was a multicentre, double-blind study in which over 8,000 postmenopausal women with hormone receptor-positive early breast cancer were randomised to one of the following treatments:

A. tamoxifen for 5 years; B. {Invented Name} for 5 years; C. tamoxifen for 2 years followed by {Invented Name} for 3 years; D. {Invented Name} for 2 years followed by tamoxifen for 3 years.

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

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

Data in Table 4 reflect the results of the Primary Core Analysis (PCA) based on data from the monotherapy arms (A and B) and from the two switching arms (C and D) at a median treatment duration of 24 months and a median follow-up of 26 months-and at a median treatment duration of 32 months and a median follow-up of 60 months.

The 5-year DFS rates were 84% for {Invented Name} and 81.4% for tamoxifen.

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

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

HR = Hazard ratio; CI = Confidence interval

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

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

Results at a median follow-up of 73 months (monotherapy arms only)

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

Table 5 Monotherapy Arms Analysis: Disease-free and overall survival at a median follow-up of 73 months (ITT population)

	{Invented Name}	Tamoxifen N=2459	Hazard Ratio ¹ (95% CI)	P Value
Disease-free survival events (primary) ²	509	565	0.88 (0.78, 0.99)	0.03
Time to distant metastasis (secondary)	257	298	0.85 (0.72, 1.00)	0.045
Overall survival (secondary) - deaths	303	343	0.87 (0.75, 1.02)	0.08
Censored analysis of DFS ³	509	543	0.85 (0.75, 0.96)	
Censored analysis of OS ³	303	338	0.82 (0.70, 0.96)	

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

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

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

Sequential Treatments Analysis (STA)

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

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

	N	Number of events ¹	Hazard ratio ²	(97.5% confidence interval)	Cox model P-value
[Letrozole →]Tamoxifen	1460	160	0.92	(0.72, 1.17)	0.42
Letrozole	1463	178			

¹ Protocol definition, including second non-breast primary malignancies, after switch / beyond two years

² Adjusted by chemotherapy use

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

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

	Letrozole → Tamoxifen	Letrozole
Number of patients	1540	1546
Number of patients with DFS events (protocol definition)	236	248
Hazard ratio ¹ (99% CI)	0.96 (0.76, 1.21)	
	Letrozole → Tamoxifen	Tamoxifen ²
Number of patients	1540	1548
Number of patients with DFS events (protocol definition)	236	269
Hazard ratio ¹ (99% CI)	0.87 (0.69, 1.09)	

¹ Adjusted by chemotherapy use (yes/no)

² 624 (40%) patients selectively crossed to letrozole after tamoxifen arm unblinded in 2005

Study D2407

Study D2407 is an open-label, randomised, multicentre post approval safety study designed to compare the effects of adjuvant treatment with letrozole and tamoxifen on bone mineral density (BMD) and serum

lipid profiles. A total of 262 patients were assigned either letrozole for 5 years or tamoxifen for 2 years followed by letrozole for 3 years.

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

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

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

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

Median total cholesterol levels in the tamoxifen arm were decreased by 16% after 6 months compared to baseline and this decrease was maintained at subsequent visits up to 24 months. In the letrozole arm, total cholesterol levels were relatively stable over time, giving a statistically significant difference in favor of tamoxifen at each time point.

Extended adjuvant treatment (MA-17)

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

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

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

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

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

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

	Median follow-up 28 months			Median follow-up 62 months		
	Letrozole N=2582	Placebo N=2586	HR (95% CI) ² P value	Letrozole N=2582	Placebo N=2586	HR (95% CI) ² P value
Disease-free survival ³						
Events	92 (3.6%)	155 (6.0%)	0.58 (0.45, 0.76) 0.00003	209 (8.1%)	286 (11.1%)	0.75 (0.63, 0.89)
4-year DFS rate	94.4%	89.8%		94.4%	91.4%	
Disease-free survival, including deaths from any cause ³						
Events	122 (4.7%)	193 (7.5%)	0.62 (0.49, 0.78)	344 (13.3%)	402 (15.5%)	0.89 (0.77, 1.03)
5-year DFS rate	90.5%	80.8%		88.8%	86.7%	
Distant metastases						
Events	57 (2.2%)	93 (3.6%)	0.61 (0.44, 0.84)	142 (5.5%)	169 (6.5%)	0.88 (0.70, 1.10)
Overall survival						
Deaths	51 (2.0%)	62 (2.4%)	0.82 (0.56, 1.19)	236 (9.1%)	232 (9.0%)	1.13 (0.95, 1.36)
Deaths ⁴	--	--	--	236 ⁵ (9.1%)	170 ⁶ (6.6%)	0.78 (0.64, 0.96)

HR = Hazard ratio; CI = Confidence Interval

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

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

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

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

⁵ Median follow-up 62 months.

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

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

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

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

Neoadjuvant treatment

A double blind trial (P024) was conducted in 337 postmenopausal breast cancer patients randomly allocated either {Invented Name} 2.5 mg for 4 months or tamoxifen for 4 months. At baseline all patients

had tumours stage T2-T4c, N0-2, M0, ER and/or PgR positive and none of the patients would have qualified for breast-conserving surgery. Based on clinical assessment there were 55% objective responses in the {Invented Name} arm versus 36% for the tamoxifen arm ($P<0.001$). This finding was consistently confirmed by ultrasound ({Invented Name} 35% vs tamoxifen 25%, $P=0.04$) and mammography ({Invented Name} 34% vs tamoxifen 16%, $P<0.001$). In total 45% of patients in the {Invented Name} group versus 35% of patients in the tamoxifen group ($P=0.02$) underwent breast-conserving therapy). During the 4-month pre-operative treatment period, 12% of patients treated with {Invented Name} and 17% of patients treated with tamoxifen had disease progression on clinical assessment.

First-line treatment

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

The results are summarised in Table 9:

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

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

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

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

{Invented Name} 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). The absence of an advantage for {Invented Name} on overall survival could be explained by the crossover design of the study.

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 ($P=0.002$).

Male breast cancer

Use of {Invented Name} in men with breast cancer has not been studied.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

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

Biotransformation

Metabolic clearance to a pharmacologically inactive carbinol metabolite is the major elimination pathway of letrozole ($CL_m = 2.1$ l/h) but is relatively slow when compared to hepatic blood flow (about 90 l/h). The cytochrome P450 isoenzymes 3A4 and 2A6 were found to be capable of converting letrozole to this metabolite. Formation of minor unidentified metabolites and direct renal and faecal excretion play only a minor role in the overall elimination of letrozole. Within 2 weeks after administration of 2.5 mg ^{14}C -labelled letrozole to healthy postmenopausal volunteers, $88.2 \pm 7.6\%$ 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 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.

Special populations

Eldery

Age had no effect on the pharmacokinetics of letrozole.

Renal impairment

In a study involving 19 volunteers with varying degrees of renal function (24-hour creatinine clearance 9-116 ml/min) no effect on the pharmacokinetics of letrozole was found after a single dose of 2.5 mg.

Hepatic impairment

In a similar study involving subjects with varying degrees of hepatic function, the mean AUC values of the volunteers with moderate hepatic impairment (Child-Pugh B) was 37% higher than in normal subjects, but still within the range seen in subjects without impaired function. In a study comparing the pharmacokinetics of letrozole after a single oral dose in eight male subjects with liver cirrhosis and severe hepatic impairment (Child-Pugh C) to those in healthy volunteers (N=8), AUC and $t_{1/2}$ increased by 95 and 187%, respectively. Thus, {Invented Name} should be administered with caution to patients with severe hepatic impairment and after consideration of the risk/benefit in the individual patient.

5.3 Preclinical safety data

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

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

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

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal

[To be completed nationally]

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

PACKAGE LEAFLET

Package leaflet: Information for the user

{Invented name} and associated names (see Annex I) strength pharmaceutical form [See Annex I - To be completed nationally]

Letrozole

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What {Invented Name} is and what it is used for
2. What you need to know before you take {Invented Name}
3. How to take {Invented Name}
4. Possible side effects
5. How to store {Invented Name}
6. Contents of the pack and other information

1. What {Invented Name} is and what it is used for

What {Invented Name} is and how it works

{Invented Name} contains an active substance called letrozole. It belongs to a group of medicines called aromatase inhibitors. It is a hormonal (or “endocrine”) breast cancer treatment. Growth of breast cancer is frequently stimulated by oestrogens which are female sex hormones. {Invented Name} reduces the amount of oestrogen by blocking an enzyme (“aromatase”) involved in the production of oestrogens and therefore may block the growth of breast cancer that needs oestrogens to grow. As a consequence tumour cells slow or stop growing and/or spreading to other parts of the body.

What {Invented Name} is used for

{Invented Name} is used to treat breast cancer in women who have gone through menopause i.e cessation of periods.

It is used to prevent cancer from happening again. It can be used as first treatment before breast cancer surgery in case immediate surgery is not suitable or it can be used as first treatment after breast cancer surgery or following five years treatment with tamoxifen. {Invented Name} is also used to prevent breast tumour spreading to other parts of the body in patients with advanced breast cancer.

If you have any questions about how {Invented Name} works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you take {Invented Name}

Follow all the doctor’s instructions carefully. They may differ from the general information in this leaflet.

Do not take {Invented Name}

- if you are allergic to letrozole or to any of the other ingredients of this medicine (listed in section 6),
- if you still have periods, i.e. if you have not yet gone through the menopause,

- if you are pregnant,
- if you are breast-feeding.

If any of these conditions apply to you, **do not take this medicine and talk to your doctor.**

Warnings and precautions

Talk to your doctor or pharmacist before taking {Invented Name}

- if you have a severe kidney disease,
- if you have a severe liver disease,
- if you have a history of osteoporosis or bone fractures (see also “Follow-up during {Invented Name} treatment” in section 3).

If any of these conditions apply to you, **tell your doctor.** Your doctor will take this into account during your treatment with {Invented Name}.

Children and adolescents (below 18 years)

Children and adolescents should not use this medicine.

Older people (age 65 years and over)

People aged 65 years and over can use this medicine at the same dose as for other adults.

Other medicines and {Invented Name}

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Pregnancy, breast-feeding and fertility

- You should only take {Invented Name} when you have gone through the menopause. However, your doctor should discuss with you about using effective contraceptive, as you may still have the potential to become pregnant during treatment with {Invented Name}.
- You must not take {Invented Name} if you are pregnant or breast feeding as it may harm your baby.

Driving and using machines

If you feel dizzy, tired, drowsy or generally unwell, do not drive or operate any tools or machines until you feel normal again.

{Invented Name} contains lactose

{Invented Name} contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take {Invented Name}

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The usual dose is one tablet of {Invented Name} to be taken once a day. Taking {Invented Name} at the same time each day will help you remember when to take your tablet.

The tablet can be taken with or without food and should be swallowed whole with a glass of water or another liquid.

How long to take {Invented Name}

Continue taking {Invented Name} every day for as long as your doctor tells you. You may need to take it for months or even years. If you have any questions about how long to keep taking {Invented Name}, talk to your doctor.

Follow-up during {Invented Name} treatment

You should only take this medicine under strict medical supervision. Your doctor will regularly monitor your condition to check whether the treatment is having the right effect.

{Invented Name} may cause thinning or wasting of your bones (osteoporosis) due to the reduction of oestrogens in your body. Your doctor may decide to measure your bone density (a way of monitoring for osteoporosis) before, during and after treatment.

If you take more {Invented Name} than you should

If you have taken too much {Invented Name}, or if someone else accidentally takes your tablets, contact a doctor or hospital for advice immediately. Show them the pack of tablets. Medical treatment may be necessary.

If you forget to take {Invented Name}

- If it is almost time for your next dose (e.g. within 2 or 3 hours), skip the dose you missed and take your next dose when you are meant to.
- Otherwise, take the dose as soon as you remember, and then take the next tablet as you would normally.
- Do not take a double dose to make up for the one that you missed.

If you stop taking {Invented Name}

Do not stop taking {Invented Name} unless your doctor tells you to. See also the section above “How long to take {Invented Name}”.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most of the side effects are mild to moderate and will generally disappear after a few days to a few weeks of treatment.

Some of these side effects, such as hot flushes, hair loss or vaginal bleeding, may be due to the lack of oestrogens in your body.

Do not be alarmed by this list of possible side effects. You may not experience any of them.

Some side effects could be serious:

Rare or uncommon side effects (i.e. they may affect between 1 to 100 in every 10,000 patients):

- Weakness, paralysis or loss of feeling in any part of the body (particularly arm or leg), loss of coordination, nausea, or difficulty speaking or breathing (sign of a brain disorder, e.g. stroke).
- Sudden oppressive chest pain (sign of a heart disorder).
- Difficulty breathing, chest pain, fainting, rapid heart rate, bluish skin discoloration, or sudden arm, leg or foot pain (signs that a blood clot may have formed).
- Swelling and redness along a vein which is extremely tender and possibly painful when touched.
- Severe fever, chills or mouth ulcers due to infections (lack of white blood cells).
- Severe persistent blurred vision.

If any of the above occurs, tell your doctor straight away.

You should also inform the doctor straight away if you experience any of the following symptoms during treatment with {Invented Name}:

- Swelling mainly of the face and throat (signs of allergic reaction).
- Yellow skin and eyes, nausea, loss of appetite, dark-coloured urine (signs of hepatitis).
- Rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever (signs of skin disorder).

Some side effects are very common. These side effects may affect more than 10 in every 100 patients.

- Hot flushes
- Increased level of cholesterol (hypercholesterolaemia)
- Fatigue
- Increased sweating
- Pain in bones and joints (arthralgia)

If any of these affects you severely, tell your doctor.

Some side effects are common. These side effects may affect between 1 to 10 in every 100 patients.

- Skin rash
- Headache
- Dizziness
- Malaise (generally feeling unwell)
- Gastrointestinal disorders such as nausea, vomiting, indigestion, constipation, diarrhoea
- Increase in or loss of appetite
- Pain in muscles
- Thinning or wasting of your bones (osteoporosis), leading to bone fractures in some cases (see also “Follow-up during {Invented Name} treatment” in section 3)
- Swelling of arms, hands, feet, ankles (oedema)
- Depression
- Weight increase
- Hair loss
- Raised blood pressure (hypertension)
- Abdominal pain
- Dry skin
- Vaginal bleeding

If any of these affects you severely, tell your doctor.

Other side effects are uncommon. These side effects may affect between 1 to 10 in every 1,000 patients.

- Nervous disorders such as anxiety, nervousness, irritability, drowsiness, memory problems, somnolence, insomnia
- Impairment of sensation, especially that of touch
- Eye disorders such as blurred vision, eye irritation
- Palpitations, rapid heart rate
- Skin disorders such as itching (urticaria)
- Vaginal discharge or dryness
- Joint stiffness (arthritis)
- Breast pain
- Fever
- Thirst, taste disorder, dry mouth
- Dryness of mucous membranes
- Weight decrease
- Urinary tract infection, increased frequency of urination
- Cough
- Increased level of enzymes

If any of these affects you severely, tell your doctor.

If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet.

5. How to store {Invented Name}

[To be completed nationally]

6. Contents of the pack and other information

What {Invented Name} contains

- The active substance is letrozole. Each film-coated tablet contains 2.5 mg letrozole.
- The other ingredients are [To be completed nationally]

What {Invented Name} looks like and contents of the pack

[To be completed nationally]

Marketing Authorisation Holder and Manufacturer

[See Annex I – To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

[See Annex I – To be completed nationally]

This leaflet was last revised in {MM/YYYY}.

[To be completed nationally]