

LETROLE



1. Product Name

Letrole 2.5 mg film coated tablet.

2. Qualitative and Quantitative Composition

Each film coated tablet contains 2.5 mg of letrozole.

Each film coated tablet contains 61.5 mg of lactose monohydrate. For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Dark yellow, capsule shape, film-coated, slightly biconvex tablet, debossed with "LZ 2.5" on one side and "G" on the other.

4. Clinical Particulars

4.1 *Therapeutic indications*

- Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.
- Extended adjuvant treatment of early breast cancer in post-menopausal women who have received ≥ 4.5 and ≤ 6.0 years prior standard adjuvant tamoxifen therapy.
- First-line treatment in postmenopausal women with advanced breast cancer.
- Treatment of advanced breast cancer in women with natural or artificially induced postmenopausal status, who have previously been treated with anti-oestrogens.

4.2 *Dose and method of administration*

Dose

The recommended dose of Letrole is 2.5 mg once daily.

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

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

Special populations

Elderly

No dose adjustment is required for elderly patients.

Hepatic and/or renal impairment

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

Paediatric

Not applicable.

Method of administration

Tablets to be swallowed whole. Do not halve the tablet. Dose equivalence when the tablet is divided has not been established.

4.3 Contraindications

- Known hypersensitivity to the active substance letrozole or to any of the excipients listed in section 6.1.
- Premenopausal endocrine status.
- Pregnancy (see sections 4.6 and 5.3).
- Breast-feeding (see sections 4.6 and 5.3).

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 Letrole. Only women of postmenopausal endocrine status should receive letrozole.

Renal impairment

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

Hepatic impairment

In patients with severe hepatic cirrhosis 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).

Bone effects

Letrozole is a potent oestrogen-lowering agent. Women with a history of osteoporosis and/or bone 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 letrozole 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, Letrole 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 medicines 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 letrozole in combination with other anti-cancer 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 CYP2A6 and, moderately, CYP2C19, but the clinical relevance is unknown. Caution is therefore indicated when giving letrozole concomitantly with medicinal products whose elimination is mainly dependent on these isoenzymes and whose therapeutic index is narrow (e.g. phenytoin, clopidogrel).

4.6 Fertility, pregnancy and lactation

Women of perimenopausal status or child-bearing potential

Letrozole 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 letrozole despite a clear postmenopausal status at the start of therapy, the physician needs to discuss adequate contraception when necessary.

Pregnancy

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

Letrozole 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.

Letrozole 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

Letrole has minor influence on the ability to drive and use machines. 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

Summary of safety profile

The frequencies of adverse reactions for letrozole are mainly based on data collected from clinical trials.

Up to approximately one third of the patients treated with letrozole 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 the clinical studies were hot flushes, hypercholesterolaemia, arthralgia, fatigue, increased sweating and nausea.

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

Tabulated list of adverse reactions

The frequencies of adverse reactions for letrozole are mainly based on data from clinical trials.

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Infections and infestations	
Uncommon	Urinary tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon	Tumour pain ¹
Blood and lymphatic system disorders	
Uncommon	Leukopenia
Immune system disorders	
Not known	Anaphylactic reaction
Metabolism and nutrition disorders	
Very common	Hypercholesterolemia
Common	Decreased appetite, increased appetite
Psychiatric disorders	
Common	Depression
Uncommon	Anxiety (including nervousness), irritability
Nervous system disorders	
Common	Headache, dizziness
Uncommon	Somnolence, insomnia, memory impairment, dysaesthesia (including paraesthesia, hypoaesthesia), dysgeusia, cerebrovascular accident, carpal tunnel syndrome
Eye disorders	
Uncommon	Cataract, eye irritation, blurred vision
Cardiac disorders	
Common	Palpitations ¹

Uncommon	Tachycardia, ischaemic cardiac events (including new or worsening angina, angina requiring surgery, myocardial infarction and myocardial ischaemia)
Vascular disorders	
Very common	Hot flushes
Common	Hypertension
Uncommon	Thrombophlebitis (including superficial and deep vein thrombophlebitis)
Rare	Pulmonary embolism, arterial thrombosis, cerebral infarction
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, cough
Gastrointestinal disorders	
Common	Nausea, dyspepsia ¹ , constipation, abdominal pain, diarrhoea, vomiting
Uncommon	Dry mouth, stomatitis ¹
Hepatobiliary disorders	
Uncommon	Increased hepatic enzymes, hyperbilirubinemia, jaundice
Not known	Hepatitis
Skin and subcutaneous tissue disorders	
Very common	Hyperhidrosis
Common	Alopecia, rash (including erythematous, maculopapular, psoriaform and vesicular rash), dry skin
Uncommon	Pruritus, urticaria
Not known	Angioedema, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia
Common	Myalgia, bone pain ¹ , osteoporosis, bone fractures, arthritis
Not known	Trigger finger
Renal and urinary disorders	
Uncommon	Pollakiuria
Reproductive system and breast disorders	
Common	Vaginal haemorrhage
Uncommon	Vaginal discharge, vulvovaginal dryness, breast pain
General disorders and administration site conditions	
Very common	Fatigue (including asthenia, malaise)
Common	Peripheral oedema, chest pain
Uncommon	General oedema, mucosal dryness, thirst, pyrexia,
Investigations	
Common	Weight increased
Uncommon	Weight decreased

¹ Adverse drug reactions reported only in the metastatic setting

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

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

	Letrozole, incidence rate	Tamoxifen, incidence rate
	N=2448	N=2447

	During treatment (Median 5y)	Any time after randomization (Median 8y)	During treatment (Median 5y)	Any time after randomization (Median 8y)
Bone fracture	10.2%	14.7%	7.2%	11.4%
Osteoporosis	5.1%	5.1%	2.7%	2.7%
Thromboembolic events	2.1%	3.2%	3.6%	4.6%
Myocardial infarction	1.0%	1.7%	0.5%	1.1%
Endometrial hyperplasia / endometrial cancer	0.2%	0.4%	2.3%	2.9%

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

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

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

* Significantly less than with letrozole monotherapy
** Significantly more than with letrozole 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 letrozole 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 letrozole (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 letrozole 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 letrozole, compared with 3 years for placebo.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Isolated cases of overdose with letrozole have been reported.

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

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

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 (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 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 to 78 hours.

In postmenopausal patients with advanced breast cancer, daily doses of 0.1 to 5 mg suppressed plasma concentrations of oestradiol, oestrone, and oestrone sulphate by 75 to 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-hydroxy-progesterone and ACTH or in plasma renin activity among postmenopausal patients treated with a daily dose of 0.1 to 5 mg letrozole. The ACTH stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 2.5 mg and 5 mg letrozole did not indicate any attenuation of aldosterone or cortisol production. Thus, glucocorticoid and mineralocorticoid supplementation is not necessary.

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

Clinical efficacy and safety

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. 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

This study was designed to investigate two primary questions: whether letrozole 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 efficacy endpoints were time to distant metastasis (TDM), overall survival (OS), distant disease-free survival (DDFS), systemic disease-free survival (SDFS), invasive contralateral breast cancer and time to breast cancer recurrence.

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

Data in Table 4 reflects 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 letrozole 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		
	Letrozole N=4003	Tamoxifen N=4007	HR ¹ (95% CI) <i>P</i>	Letrozole N=4003	Tamoxifen N=4007	HR ¹ (95% CI) <i>P</i>
Disease-free survival (primary) - events (protocol definition ²)	351	428	0.81 (0.70,0.93) 0.003	585	664	0.86 (0.77,0.96) 0.008
Overall survival (secondary) Number of deaths	166	192	0.86 (0.70,1.06)	330	374	0.87 (0.75,1.01)

HR = Hazard ratio; CI = Confidence interval

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

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

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

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

Table 5. Monotherapy arms analysis: disease-free and overall survival at a median follow-up of 96 months (ITT population)

	Letrozole N=2463	Tamoxifen N=2459	Hazard Ratio ¹ (95% CI)	P Value
Disease-free survival events (primary) ²	626	698	0.87 (0.78, 0.97)	0.01
Time to distant metastasis (secondary)	301	342	0.86 (0.74, 1.01)	0.06
Overall survival (secondary) - deaths	393	436	0.89 (0.77, 1.02)	0.08
Censored analysis of DFS ³	626	649	0.83 (0.74, 0.92)	
Censored analysis of OS ³	393	419	0.81 (0.70, 0.93)	

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

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

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

Sequential treatments analyses (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	254	1.03	(0.84, 1.26)	0.72
Letrozole	1464	249			

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

² Adjusted by chemotherapy use

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

Table 7. Sequential treatments analyses from randomisation (STA-R) of disease-free survival (ITT STA-R population)

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

¹ Adjusted by chemotherapy use (yes/no)

² 626 (40%) patients selectively crossed to letrozole after tamoxifen arm unblinded in 2005

Study D2407

Study D2407 is an open-label, randomized, 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 postmenopausal women with hormone sensitive resected primary breast cancer were randomly 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 (L2-L4) BMD showed a median decrease of 4.1% for letrozole compared to a median increase of 0.3% for tamoxifen. No patient with a normal BMD at baseline became osteoporotic during 2 years of treatment and only 1 patient with osteopenia at baseline (T score of -1.9) developed osteoporosis during the treatment period (assessment by central review).

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

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

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

Extended adjuvant treatment (MA-17)

In a multicentre, double-blind, randomized, 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 letrozole 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 the patients being followed-up for up to 38 months) showed that letrozole significantly reduced the risk of breast cancer recurrence by 42% compared with placebo (hazard ratio 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: (letrozole 51 deaths; placebo 62; HR 0.82; 95% CI 0.56, 1.19).

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

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

	Median follow-up 28 months ¹			Median follow-up 62 months		
	Letrozole	Placebo	HR (95% CI) ²	Letrozole	Placebo	HR (95% CI) ²
	N=2582	N=2586	P value	N=2582	N=2586	P value
Disease-free survival (protocol definition)³						
Events	92 (3.6%)	155 (6.0%)	0.58 (0.45, 0.76) 0.00003	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 survival³, including deaths from any cause						
Events	122 (4.7%)	193 (7.5%)	0.62 (0.49, 0.78)	344 (13.3%)	402 (15.5%)	0.89 (0.77, 1.03)
5-year DFS rate	90.5%	80.8%		88.8%	86.7%	
Distant metastases						
Events	57 (2.2%)	93 (3.6%)	0.61 (0.44, 0.84)	142 (5.5%)	169 (6.5%)	0.88 (0.70, 1.10)
Overall survival						
Deaths	51 (2.0%)	62 (2.4%)	0.82 (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 = 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 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 letrozole 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 letrozole 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.

First-line treatment

One controlled double-blind trial was conducted comparing letrozole 2.5 mg to tamoxifen 20 mg as first-line therapy in postmenopausal women with advanced breast cancer. The percentage of

patients with hormone receptor positive tumours was 64% in the letrozole group and 67% in the tamoxifen group. In 907 women, letrozole was superior to tamoxifen in time to progression (primary endpoint) and in overall objective tumour 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	Letrozole 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 letrozole and 6.4 months for tamoxifen in patients with soft tissue disease only and median 8.3 months for letrozole 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 (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). The absence of an advantage for letrozole 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).

Neoadjuvant treatment of breast cancer

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

Male breast cancer

Use of letrozole 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/L fasted versus 98.7 ± 18.6 nmol/L fed), but the extent of absorption (AUC) is not changed. The minor effect on the absorption rate is not considered to be of clinical relevance, and therefore letrozole may be taken without regard to meal times.

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 P_{450} 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.

Elimination

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

Linearity/non-linearity

The pharmacokinetics of letrozole were dose proportional after single oral doses up to 10 mg (dose range: 0.01 to 30 mg) and after daily doses up to 1.0 mg (dose range: 0.1 to 5 mg). After a 30 mg single, oral dose there was a slightly dose over-proportional increase in AUC value. The dose over-proportionality is likely to be the result of a saturation of metabolic elimination processes. Steady levels were reached after 1 to 2 months at all dosage regimens tested (0.1 to 5.0 mg daily).

Special Populations

Elderly

Age had no effect on the pharmacokinetics of letrozole.

Renal impairment

In a study involving 19 volunteers with varying degrees of renal function (24-hour creatinine clearance 9 to 116 mL/min), no effect on the pharmacokinetics of letrozole was found after a single dose of 2.5 mg. In addition to the above study assessing the influence of renal impairment on letrozole, a covariate analysis was performed on the data of two pivotal studies. Calculated creatinine clearance (CL_{cr}) [Study 1 range: 19 to 187 mL/min; Study 2 range: 10 to 180 mL/min] showed no statistically significant association between letrozole plasma trough levels at steady-state (C_{min}). Furthermore, data of these studies in second-line metastatic breast cancer showed no evidence of an adverse effect of letrozole on CL_{cr} or an impairment of renal function. Therefore, no dose adjustment is required for patients with renal impairment (CL_{cr} ≥ 10 mL/min). Little information is available in patients with severe impairment of renal function (CL_{cr} <10 mL/min).

Hepatic impairment

In a similar study involving subjects with varying degrees of hepatic function, the mean AUC values of the volunteers with moderate hepatic impairment (Child-Pugh score B) was 37% higher than in normal subjects, but still within the range seen in subjects without impaired function. In a study comparing the pharmacokinetics of letrozole after a single oral dose in eight subjects with liver cirrhosis and severe hepatic 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 to patients with severe hepatic impairment and after consideration of the risk/benefit in the individual patient.

5.3 Preclinical safety data

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

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

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

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

Both *in vitro* and *in vivo* investigations 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.

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

Letrozole was embryotoxic and fetotoxic 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 4.4).

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

6. Pharmaceutical Particulars

6.1 *List of excipients*

Tablet core:

- lactose monohydrate
- microcrystalline cellulose
- maize starch
- sodium starch glycollate
- magnesium stearate
- colloidal silicon dioxide.

Tablet film coating:

- hypromellose
- polydextrose
- triacetin
- macrogol
- iron oxide yellow (E172)
- quinoline yellow aluminium lake (E104)
- iron oxide red (E172)
- titanium dioxide.

Letrole does not contain sucrose, gluten or tartrazine.

6.2 *Incompatibilities*

Not applicable.

6.3 *Shelf life*

3 years

6.4 *Special precautions for storage*

Store at or below 25°C.

6.5 *Nature and contents of container*

PVC/PVdC/Aluminium blister. Pack size of 30 film-coated tablets.

6.6 *Special precautions for disposal*

No special requirements for disposal.

7. Medicines Schedule

Prescription medicine

8. Sponsor Details

Mylan New Zealand Ltd
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Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

1 April 2010

10. Date of Revision of the Text

26 June 2019

Summary table of changes

Section	Summary of new information
4.3 & 4.6	Changed lactation to breast-feeding.
4.4	Included under other warnings that Letrole not recommended for patients with rare hereditary problems of galactose intolerance, of severe lactase deficiency or of glucose-galactose malabsorption.
4.8	Clarified that frequencies of adverse reactions are mainly based on data from clinical trials.
4.8	Revised frequency of palpitations and arthritis from uncommon to common in Table 1. Addition of hyperbilirubinemia and jaundice as uncommon adverse reactions in Table 1. Addition of chest pain as common adverse reaction in Table 1. Reworded some sections.
6.1	Changed format to bullet points for list of excipients
All	Minor rewording and administration changes.