# New Zealand Data Sheet

## 1. PRODUCT NAME

LETARA® 2.5 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each LETARA 2.5 mg tablet contains 2.5 mg letrozole.

**Excipient(s) with known effect**

LETARA 2.5 mg tablets contain lactose monohydrate. For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

LETARA 2.5 mg tablets are yellow to dark yellow round, film coated, biconvex tablet, engraved with 'L' on one face and plain on the other.

Do not halve tablet. Dose equivalence when the tablet is divided has not been established.

## 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 antioestrogens.

### 4.2. Dose and method of administration

**Dose**

***Adults***

The recommended dose of LETARA is 2.5 mg once daily. In the adjuvant and extended adjuvant setting, treatment with LETARA should continue for 5 years or until tumour relapse occurs, whichever comes first. In patients with metastatic disease, treatment with LETARA should continue until tumour progression is evident.

No dose adjustment is required for elderly patients.

***Special populations***

Patients with hepatic and/or renal impairment

No dosage adjustment is required for patients with mild to moderate hepatic insufficiency (Child-Pugh A or B) or renal impairment (creatinine clearance ≥ 10 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 4.4 and 5.2).

***Paediatric population***

LETARA is not recommended for use in children and adolescents. The safety and efficacy of LETARA 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.

**Method of Administration**

LETARA should be administered once daily.

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

A missed dose should be taken as soon as the patient remembers. However, if it is almost time for the next dose (within 2 or 3 hours), the missed dose should be skipped, and the patient should go back to her regular dosage schedule. Doses should not be doubled because with daily doses over the 2.5 mg recommended dose, over-proportionality in systemic exposure was observed (see section 5.2)

## 4.3. Contraindications

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

## Renal impairment

Letrozole has not been investigated in patients with creatinine clearance <10 mL/min nor in a sufficient number of patients with a creatinine clearance less than 30 mL/min. The potential risk/benefit to such patients should be carefully considered before administration of letrozole. As letrozole is weakly bound to plasma proteins (see section 5.2), it is anticipated that it could be removed from circulation by dialysis. Similar caution should be exercised in patients with severe hepatic insufficiency.

## 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. Osteoporosis and/or bone fractures have been reported with the use of letrozole. Therefore, 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).

## Tendon disorders

Tenosynovitis and tendonitis have been reported in association with the use of third generation aromatase inhibitors. Cases of tendon rupture have also been reported. Close monitoring of the patients and appropriate measures (e.g. immobilisation) must be initiated for the affected tendon (see section 4.8).

## 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, LETARA is not recommended for patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.

LETARA contains sodium. This medicine contains less than 1 mmol sodium per tablet, that is to say essentially "sodium free".

## 4.5. Interaction with other medicines and other forms of interaction

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

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

There is no clinical experience to date on the use of 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.

Letrozole inhibits in vitro the cytochrome P450-isozymes 2A6, and moderately 2C19. CYP2A6 does not play a major role in drug metabolism. In *in vitro* experiments letrozole, was not able to substantially inhibit the metabolism of diazepam (a substrate of CYP2C19) at concentrations approximately 100-fold higher than those observed in plasma at steady state. Thus, clinically relevant interactions with CYP2C19 are unlikely to occur. However, caution should be used in the concomitant administration of drugs whose disposition is mainly dependent on these isoenzymes and whose therapeutic index is narrow.

## 4.6. Fertility, pregnancy and lactation

### Women of perimenopausal status or childbearing 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. Letrozole is contraindicated during pregnancy (see section 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 lactation (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

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, as adjuvant treatment of early breast cancer and as extended adjuvant treatment in women who have received prior standard tamoxifen therapy. Approximately one third of the patients treated with Letrozole in the metastatic and neoadjuvant settings, approximately 70 to 75% of the patients in the adjuvant setting (both letrozole and tamoxifen arms), and approximately 40% of the patients 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, and most are associated with oestrogen deprivation.

The most frequently reported adverse reactions in the clinical studies were hot flushes, hypercholesterolaemia, arthralgia, nausea, increased sweating, and fatigue. Many adverse reactions can be attributed to the normal pharmacological consequences of oestrogen deprivation (e.g. hot flushes, alopecia and vaginal bleeding). The following adverse drug reactions, listed in Table 1, were reported from clinical studies and from post marketing experience with letrozole.

In the adjuvant settings there was a significant difference in incidence of osteoporosis and bone fractures in patients who received letrozole compared to patients who received tamoxifen (osteoporosis 2.0% vs 1.1%, P=0.001 and bone fractures 6.4% vs 4.8%, P=0.003 at any time after randomization, respectively).

In the extended adjuvant setting there was a higher but non-significant incidence of osteoporosis and bone fractures in patients who received letrozole than in patients who received placebo (6.9% vs 5.5% and 5.9% vs 5.5% respectively) (see section 5.1).

**Table 1** Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000), including isolated report.

| | |
|---|---|
| **Infections and infestations**<br>Uncommon | <br>Urinary tract infection |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)**<br>Uncommon | <br>Tumour pain |
| **Blood and the lymphatic system disorders**<br>Uncommon | <br>Leukopenia |
| **Immune system disorders**<br>Not known | <br>Anaphylactic reaction |
| **Metabolism and nutrition disorders**<br>Very Common<br>Common | <br>Hypercholesterolemia<br>Anorexia, appetite increase |
| **Psychiatric disorders**<br>Common<br>Uncommon | <br>Depression<br>Anxiety (including nervousness), irritability |
| **Nervous system disorders**<br>Common<br>Uncommon | <br>Headache, dizziness<br>Somnolence, insomnia, memory impairment, dysaesthesia (including paraesthesia, hypoaesthesia), taste disturbance, cerebrovascular accident, carpal tunnel syndrome |
| **Eye disorders**<br>Uncommon | <br>Cataract, eye irritation, blurred vision |
| **Cardiac disorders**<br>Common<br><br>Uncommon | <br>Palpitations[1]<br><br>Tachycardia, ischaemic cardiac events (including new or worsening angina, angina requiring surgery, myocardial infarction and myocardial ischaemia) |
| **Vascular disorders**<br><br>Very common<br>Common<br><br>Uncommon<br><br><br><br>Rare | <br><br>Hot flushes<br>Hypertension<br><br>Thrombophlebitis (including superficial and deep vein thrombophlebitis)<br><br>Pulmonary embolism, arterial thrombosis, cerebrovascular infarction |

| | |
|---|---|
| **Respiratory, thoracic and mediastinal disorders** | |
| Uncommon | Dyspnoea, cough |
| **Gastrointestinal disorders** | |
| Common | Nausea, vomiting, dyspepsia[1], constipation, diarrhoea, abdominal pain |
| Uncommon | Stomatitis[1], dry mouth |
| **Hepatobiliary disorders** | |
| Uncommon | Increased hepatic enzymes, hyperbilirubinemia, jaundice |
| Unknown | Hepatitis |
| **Skin and subcutaneous tissue disorders** | |
| Very common | Hyperhidrosis (increased sweating) |
| Common | Alopecia, rash (including erythematous, maculopapular, psoriaform and vesicular rash), dry skin |
| Uncommon | Pruritus, urticaria |
| Unknown | Angioedema, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders** | |
| Very common | Arthralgia |
| Common | Myalgia, bone pain[1], osteoporosis, bone fractures, arthritis |
| Uncommon | Tendonitis |
| Rare | Tendon rupture |
| Unknown | Trigger finger, tenosynovitis |
| **Renal and urinary disorders** | |
| Uncommon | Increased urinary frequency |
| **Reproductive system and breast disorders** | |
| Common | Vaginal bleeding |
| 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, pyrexia, mucosal dryness, thirst |
| **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.

***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 reactions https://nzphvc.otago.ac.nz/reporting/

### 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## 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 stimulatory effects 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 cytochrome $P_{450}$ subunit of the enzyme, 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 to 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 suppress plasma concentration 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 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 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 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.

## Clinical efficacy and safety

### *Adjuvant treatment*

A multicentre, double-blind study randomized over 8,000 postmenopausal women with resected receptor-positive early breast cancer, to one of the following arms:

- A. tamoxifen for 5 years
- B. 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

Data in Table 2 reflect results from non-switching arms (arms A and B) together with data truncated 30 days after the switch in the two switching arms (arms C and D). 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% (1,252 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 tumour or death from any cause. Letrozole reduced the risk of recurrence by 19% compared with tamoxifen (hazard ratio 0.81; P=0.003), corresponding to a reduction of the absolute risk by 2.6% at 5 years. 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) and reduced the risk of invasive contralateral breast cancer by almost 40% but due to the relatively low power of so few events, this result was not statistically significant. 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 summarise the results:

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

| | **Letrozole N=4003** | **Tamoxifen N=4007** | **Hazard Ratio (95% CI)** | **P-value[1]** |
|---|---|---|---|---|
| *Disease-free survival (primary)* -events (protocol definition, total) | 351 | 428 | 0.81 (0.70, 0.93) | 0.0030 |
| *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

| | **Hazard Ratio, (95% CI)** | **P-value[1]** |
|---|---|---|
| *Disease-free survival* | | |
| **Nodal status** | | |
| Positive | 0.71 (0.59, 0.85) | 0.0002 |
| Negative | 0.72 (0.55, 0.95) | 0.8875 |

| | | |
|---|---|---|
| **Prior adjuvant chemotherapy** | | |
| Yes | 0.72 (0.55, 0.95) | 0.0178 |
| 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*

### *Extended adjuvant treatment*

In a multicentre, double-blind, randomized, 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 for 5 years.

The primary analysis conducted at a median follow-up of around 28 months (25% of the patients being followed-up for up to 38 months) showed that letrozole reduced the risk of breast cancer recurrence by 42% compared with placebo (hazard ratio 0.58; P=0.00003). Sensitivity analysis confirmed the robustness of the data. The statistically significant benefit in DFS in favour of letrozole was observed regardless of nodal status - node negative, hazard ratio 0.48, P=0.002; node positive, hazard ratio 0.61, P=0.002.

For the secondary endpoint overall survival (OS) a total 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). In node positive disease, Letrozole significantly reduced the risk of mortality by approximately 40 % (hazard ratio 0.61; P=0.035), whereas no significant difference was seen in node negative patients (hazard ratio 1.36; P=0.385), in patient with prior chemotherapy and in patients with no prior chemotherapy. See Tables 4 and 5 that summarize the results:

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

| | **Letrozole N=2582** | **Tamoxifen N=2586** | **Hazard Ratio (95% CI)** | **P-value** |
|---|---|---|---|---|
| *Disease-free survival (primary)* -events (protocol definition, total) | 92 (3.6%) | 155 (6.0%) | 0.58 (0.45, 0.76)[1] | 0.00003 |

| | | | | |
|---|---|---|---|---|
| *Distant disease-free survival* | 57 | 93 | 0.61 (0.44, 0.84)[2] | 0.003 |
| *Overall survival (secondary)* -number of deaths (total) | 51 | 62 | 0.82 (0.56, 1.19)[1] | 0.291 |
| *Contralateral breast cancer (secondary)* | | | | |
| -including DCIS/LCIS (total) | 19 | 30 | 0.63 (0.36, 1.13)[3] | 0.0120 |
| -invasive (total) | 15 | 25 | 0.60 (0.31, 1.14)[3] | 0.117 |

*CI = confidence interval, DCIS = ductal carcinoma in situ, LCIS = lobular carcinoma* in situ

1. *Stratified by receptor status, nodal status and prior adjuvant chemotherapy*
2. *Non-stratified analysis*
3. *Odds ratio, stratified analysis*

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

| | **Hazard Ratio** | **95% CI for disease free survival** | **P-value** |
|---|---|---|---|
| *Disease-free survival* | | | |
| **Receptor status** | | | |
| Receptor positive | 0.57 | (0.44, 0.75) | 0.00003 |
| **Nodal status** | | | |
| Negative | 0.48 | (0.30, 0.78) | 0.00239 |
| Positive | 0.61 | (0.44, 0.83) | 0.00168 |
| **Chemotherapy** | | | |
| None | 0.58 | (0.40, 0.84) | 0.00330 |
| Received | 0.59 | (0.41, 0.84) | 0.00322 |
| *Overall survival* | | | |
| **Nodal status** | | | |
| Negative | 1.36 | (0.68, 2.71) | 0.385 |
| Positive | 0.61 | (0.38, 0.97) | 0.035 |

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

Updated 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. After the unblinding of the study, 56% of the patients in the placebo arm opted to switch to letrozole (i.e. late extended adjuvant population).

In this analysis of DFS, letrozole significantly reduced the risk of breast cancer recurrence compared with placebo (HR 0.68; 95% CI 0.55, 0.83; P=0.0001). Letrozole also significantly reduced the odds of a new invasive contralateral breast cancer by 41% compared with placebo (OR 0.59; 95% CI 0.36, 0.96; P=0.03). There was no significant difference in distant disease-free survival or overall survival.

The clinical interpretation of these updated analyses should take into account that over half of the patients in the placebo arm switched to letrozole. Therefore, analyses were conducted to evaluate the effect of the switch. In one exploratory analysis comparing letrozole with placebo until switch, letrozole reduced the risk of breast cancer recurrence (HR 0.55; 95% CI 0.45,0.68). After unblinding, patients who switched to letrozole from placebo had been off adjuvant tamoxifen for a median 31 months (range 14 to 79 months). Other analyses were performed within the placebo arm taking account of the switch to letrozole. Acknowledging the varying times of the switch after the completion of prior tamoxifen therapy and the known limitations of non-randomized comparison, results suggested a consistent reduction in the risk of breast cancer recurrence in those patients who switched to letrozole (HR 0.31; 95% CI 0.20, 0.49).

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 the placebo arm who switched to letrozole, a similar pattern of general adverse events was observed. The incidence of self-reported osteoporosis, any time after randomization, was higher in patients who received letrozole than for placebo (12.3% vs. 7.4%). The incidence of clinical fractures, any time after randomization, was higher in patients who received letrozole than for placebo (10.9% vs. 7.2%). In patients who switched to letrozole, newly diagnosed osteoporosis, any time after switching, was reported in 3.6% of patients while fractures were reported in 5.1% of patients any time after switching.

Updated results (median follow-up was 40 months) from the bone mineral density (BMD) sub-study demonstrated that, at 2 years, compared to baseline, patients receiving letrozole had a median decrease of 3.8% in hip BMD compared to 2.0 % in the placebo group (P=0.018). There was no significant difference in changes in lumbar spine BMD at any time. Updated results (median follow-up was approximately 50 months) from the lipid sub-study showed no significant difference between the letrozole and placebo groups at any time. In the core study the incidence of cardiovascular ischemic events for Letrozole versus placebo until switch was 11.1% vs. 8.6%.

### *First-line treatment*

One well-controlled double-blind trial was conducted comparing letrozole 2.5 mg to tamoxifen 20 mg as first-line therapy in postmenopausal women with locally advanced or metastatic breast cancer. In 907 women, letrozole was statistically significant in favour of letrozole compared with tamoxifen in time to progression (primary endpoint) and in overall objective tumour response, time to treatment failure and clinical benefit. Specific results are presented in Table 6.

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

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

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

**Table 7** Receptor status

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

*ER: oestrogen receptor*

*PgR: progesterone receptor*

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

**Table 8** Efficacy by dominant disease site

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

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

Study design allowed patients to crossover upon progression to the other therapy or discontinue from the study. Approximately 50% of patients crossed over to the opposite treatment arm and crossover was virtually completed by 36 months. The median time to crossover was 17 months (letrozole to tamoxifen) and 13 months (tamoxifen to letrozole). Letrozole treatment in the first line therapy of advanced breast cancer patients is associated with an early survival advantage over tamoxifen. The median survival was 34 months for letrozole and 30 months for tamoxifen. A significantly greater number of patients were alive on letrozole versus tamoxifen throughout the first 24 months of the study (repeated log rank test), see Table 9.

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

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

**Overall long rank test P-value.*

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

**Table 10** Results according to prior adjuvant antioestrogen therapy

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

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

The total duration of endocrine therapy (time to chemotherapy) was significantly longer for 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).

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

### *Second-line treatment*

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

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

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

### *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 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 ± 7.6 % of the radioactivity was recovered in urine and 3.8 ± 0.9% in faeces. At least 75% of the radioactivity recovered in urine up to 216 hours (84.7 ± 7.8% of the dose) was attributed to the glucuronide of the carbinol metabolite, about 9% to two unidentified metabolites, and 6% to unchanged letrozole.

The apparent terminal elimination half-life in plasma is about 2 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.

Therefore, no dose adjustment is required for patients with renal impairment (CLcr ≥ 10 mL/min). Little information is available in patients with severe impairment of renal function (CLcr < 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 t½ increased by 95 and 187%, respectively. Breast-cancer patients with severe hepatic impairment are thus expected to be exposed to higher levels of letrozole than patients without severe hepatic dysfunction. However, since in patients dosed at 5 or 10 mg/day no increase in toxicity was observed, a dose reduction in patients with severe hepatic impairment appears not to be warranted, although such patients should be kept under close supervision. In addition, in two well-controlled studies involving 359 patients with advanced breast cancer, no effect of renal impairment (calculated creatinine clearance: 20 to 50 mL/min) or hepatic dysfunction was found on the letrozole concentration.

## 5.3. Preclinical safety data

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

Letrozole showed a low degree of acute toxicity in rodents exposed to up to 2,000 mg/kg. 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 section 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

**LETARA 2.5 mg tablet** contains
Colloidal anhydrous silica, microcrystalline cellulose, lactose monohydrate, magnesium stearate, maize starch, sodium starch glycollate, hydroxypropyl methylcellulose, polyethylene glycol 8000, talc, titanium dioxide (E 171), iron oxide yellow (E 172).

### 6.2. Incompatibilities

Not applicable.

### 6.3. Shelf life

36 months.

### 6.4. Special precautions for storage

Store at or below 30°C.

### 6.5. Nature and contents of container

PVC/PVDC aluminium foil blister, 30 tablets.

### 6.6. Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

## 7. MEDICINE SCHEDULE

Prescription medicine

## 8. SPONSOR

Douglas Pharmaceuticals Ltd

P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

## 9. DATE OF FIRST APPROVAL

17 September 2009

## 10. DATE OF REVISION OF THE TEXT

19 February 2024

Summary table of changes

| Section Changed | Summary of new information |
|---|---|
| 4.4 | Updated information on tendon disorders |
| 4.8 | Updated information on tendon disorders |