

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Letzo 2.5mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5mg letrozole.

Excipients(s) with known effect

Each film-coated tablet contains 58.4 mg of lactose (as lactose monohydrate) and up to 0.21 mg (0.009 mmol) sodium (as sodium starch glycolate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablet.

Film-coated tablet, dark yellow, round, slightly biconvex with bevelled edges. One side bears the imprint "FV", the other "CG".

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 Letzo is 2.5mg once daily. No dose adjustment is required for elderly patients.

In patients with advanced or metastatic breast cancer, treatment with Letzo should continue until tumour progression is evident.

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

Paediatric population

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

Letzo should be taken orally and can be taken with or without food.

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

- 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 useMenopausal 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 Letzo. Only women of postmenopausal endocrine status should receive Letzo.

Renal Impairment

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

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

Letrozole 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).

Tendonitis and tendon rupture

Tendonitis and tendon ruptures (rare) may occur. 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 Letzo 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, Letzo is not recommended for patients with rare hereditary problems of galactose intolerance, of severe lactase deficiency or of glucose-galactose malabsorption.

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet 2.5 mg, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

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 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. Coadministration 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, clopidogrel).

4.6 Fertility, pregnancy and lactation

Women of perimenopausal status or child-bearing potential

Letzo 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 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), letrozole may cause congenital malformations when administered during pregnancy. Studies in animals have shown reproductive toxicity (see section 5.3).

Letzo 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.

Letzo 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

Letrozole 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 the 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 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 listing of adverse reactions

The frequencies of adverse reactions for letrozole 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 letrozole:

Table1

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 ($> 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), 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 | |
| Notknown: | Anaphylactic reaction |
| Metabolism and nutrition disorders | |
| Very common: | Hypercholesterolaemia |
| 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 |
| Notknown: | Hepatitis |
| Skin and subcutaneous tissue disorders | |
| Very common: | Hyperhidrosis |
| Common: | Alopecia, rash (including erythematous, maculopapular, psoriaform, and vesicular rash), dry skin |
| Uncommon: | Pruritus, urticaria |
| Notknown: | Angioedema, toxic epidermal necrolysis, erythema multiforme |
| Musculoskeletal and connective tissue disorders | |
| Verycommon: | Arthralgia |
| Common: | Myalgia, bone pain 1, osteoporosis, bone fractures, arthritis |
| Uncommon: | Tendonitis |
| Rare: | Tendon rupture |
| Not known: | Trigger finger |
| Renal and urinary disorders | |
| Uncommon: | Pollakiuria |
| Reproductive system and breast disorders | |
| Common: | Vaginal haemorrhage |
| Uncommon: | Vaginal discharge, vulvo vaginal 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 | 07% | 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Isolated cases of overdosage with letrozole have been reported.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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. 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.

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 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 | HR¹ (95% CI) <i>P</i> | Letrozole N=4003 | Tamoxifen N=4007 | HR¹ (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) | 166 | 192 | 0.86 | 330 | 374 | 0.87 |

| | | | | | | |
|------------------|--|--|--------------|--|--|--------------|
| Number of deaths | | | (0.70, 1.06) | | | (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 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 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 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 events¹ | Hazard ratio² | (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 | Tamoxifen² |
| Number of patients | 1540 | 1548 |

| | | |
|---|-------------------|-----|
| Number of patients with DFS event (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, 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 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 patients being followed up for at least 38 months), showed that letrozole 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: (letrozole 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 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 | | | Median follow-up 62 months | | |
|--|----------------------------|-------------------|----------------------------|----------------------------|-------------------|--|
| | Letrozole N=2582 | Placebo N=2586 | HR (95% CI)* P value | Letrozole N=2582 | Placebo N=2586 | HR (95% CI) ² P value |
| Disease-free survival³ | | | | | | |
| Events | 92 (3.6%) | 155 | 0.58 | 209 | 286 | 0.75 |

| | | | | | | |
|---|---------------|---------------|-------------------------|----------------------------|----------------------------|----------------------|
| | | (6.0%) | (0.45, 0.76) 0.00003 | (8.1%) | (11.1%) | (0.63, 0.89) |
| 4-year DFS rate | 94% | 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 = 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 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.

Neoadjuvant treatment

A double blind trial (P024) was conducted in 337 postmenopausal breast cancer patients randomly allocated either letrozole 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 letrozole arm versus 36% for the tamoxifen arm ($P < 0.001$). This finding was consistently confirmed by ultrasound (letrozole 35% vs tamoxifen 25%, $P = 0.04$) and mammography (letrozole 34% vs tamoxifen 16%, $P < 0.001$). In total 45% of patients in the letrozole 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 letrozole and 17% of patients treated with tamoxifen had disease progression on clinical assessment.

First-line treatment

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

The results are 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 (95% CI for median) | 9.4 months (8.9, 11.6 months) | 6.0 months (5.4, 6.3 months) |
| | Hazard ratio (HR) (95% CI for HR) <i>P</i> CR+PR | 145 (32%) | 0.72 (0.62, 0.83) <0.0001 95 (21%) |
| | (95% CI for rate) | (28, 36%) | (17, 25%) |
| | Odds ratio (95% CI for odds ratio) <i>P</i> | | 1.78 (1.32, 2.40) 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 (log rank 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 ($P=0.002$).

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/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.

Elimination

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 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 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 5mg). 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 (0.1-5.0 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 9116 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 (Study AR/BC2 and Study AR/BC3). Calculated creatinine clearance (CL_{cr}) [Study AR/BC2 range: 19 to 187 mL/min; Study AR/BC3 range: 10 to 180 mL/min] showed no statistically significant association between letrozole plasma trough levels at steady-state (C_{min}). Furthermore, data of Study AR/BC2 and Study AR/BC3 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 ($CL_{cr} \geq 10$ 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 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 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 *invitro* and *invivo* 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.

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 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

Tablet core

Lactose monohydrate
Cellulose microcrystalline (E460)
Maize starch
Sodium starch glycolate Magnesium stearate (E572)
Silica colloidal anhydrous (E551)

Film-coating:

Hypromellose (E464)
Talc (E553b)
Macrogol (PEG 8000)
Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PE/PVDC/aluminium blister packs.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

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