

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

LETROVITAE 2.5 mg film-coated tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5 mg letrozole.

Each tablet contains 45 mg of lactose monohydrate (see section 4.4)

For the full list of excipients, see section 6.1 List of excipients.

### 3. PHARMACEUTICAL FORM

Film-coated tablets

Yellow, circular, biconvex film-coated tablets plain on both sides.

### 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 state, who have previously been treated with anti-estrogens.
- 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

##### Adult and elderly patients

The recommended dose of letrozole is 2.5 mg once daily. No dose adjustment is required in elderly patients.

In patients with advanced or metastatic breast cancer, treatment with letrozole should continue until the progression of the tumor is evident.

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

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

#### Paediatric population

Letrozole is not recommended for use in children and adolescents. The safety and efficacy of letrozole in children and adolescents aged up to 17 years have not been established. Limited data are available and recommendation on a posology can be made.

#### Renal impairment

No dose adjustment of letrozole is required for patients with renal insufficiency with creatinine clearance  $\geq 10$  ml/min. Insufficient data are available in cases of renal insufficiency with a creatinine clearance lower than 10 ml/min (see sections 4.4 and 5.2).

#### Hepatic impairment

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

#### Method of administration

LETROVITAE 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 use

#### Menopausal state

In patients whose menopausal status is unclear, luteinizing hormone (LH), follicle stimulating hormone (FSH) and/or estradiol level should be measured before initiating treatment with LETROVITAE. Only women of postmenopausal endocrine state should receive letrozole.

#### Renal impairment

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

#### 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 estrogen-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 extended adjuvant and extended adjuvant treatment and monitored during and following treatment with letrozole. The treatment or prophylaxis of osteoporosis should be initiated as appropriate and carefully monitored. In 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 letrozole with tamoxifen, other antiestrogens or estrogen-containing therapies should be avoided as these substances may diminish the pharmacological action of LETROVITAE (see section 4.5).

#### Warnings on excipients

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency (failure observed in certain populations of Lapland) or glucose or galactose absorption problems should not take this medicine.

This medicine can cause allergic reactions because it contains tartrazine.

- May cause asthma, especially in patients allergic to acetylsalicylic acid.
- May cause allergic reactions such as angioedema, asthma, urticaria and anaphylactic shock.

#### Use in athletes

Patients should be warned that this medicine contains letrozol, which can produce a positive result in doping control tests.

### **4.5 Interactions with other medicinal products and other forms of interaction**

Metabolism of letrozole is partly mediated via CYP2A6 and CYP3A4. Cimetidine, a weak, unspecified 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 estrogen or other anticancer agents, other than tamoxifen. Tamoxifen, other antiestrogens or estrogen-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. The concomitant administration of letrozole with tamoxifen, other antiestrogens or estrogens should be avoided.

*In vitro*, letrozole inhibits cytochrome P450 isozymes 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 mainly on these isoenzymes and whose therapeutic index is narrow (eg phenytoin, clopidogrel).

#### **4.6 Fertility, pregnancy and lactation**

##### Women of perimenopausal state 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 state 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).

Letrozole is contraindicated during pregnancy (see sections 4.3 and 5.3).

##### Breast-feeding

It is not known 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 estrogen production by aromatase inhibitor. In premenopausal women, the inhibition of estrogen 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 security 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 experience 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, hypercholesterolemia, 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 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:

**Table 1**

Adverse reactions are ranked under headings of by frequency, the most frequent first, using the following convention: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  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).

<b>Infections and infestations</b>	
Uncommon	Urinary tract infection
<b>Neoplasms benign, malignant and unspecified (including cysts and polyps)</b>	
Uncommon	Tumour pain <sup>1</sup>
<b>Blood and lymphatic system disorders</b>	
Uncommon	Leucopenia
<b>Immune system disorders</b>	
Not known	Anaphylactic reaction
<b>Metabolism and nutrition disorders</b>	
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 paresthesia, hypoaesthesia), dysgeusia, cerebrovascular accident, carpal tunnel syndrome

**Eye disorders**

Uncommon	Cataract, eye irritation, blurred vision
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**Cardiac disorders**

Common	Palpitations <sup>1</sup>
Uncommon	Tachycardia, ischemic cardiac events (including new or worsening angina, angina requiring surgery, myocardial infarction and myocardial ischemia)

**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
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**Gastrointestinal disorders**

Common	Nausea, dyspepsia <sup>1</sup> , constipation, abdominal pain, diarrhoea, vomiting
Uncommon	dry mouth, Stomatitis <sup>1</sup>

**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
Unknown	Angioedema, toxic epidermal necrolysis, erythema multiforme

**Musculoskeletal and connective tissue disorders**

Very common	Arthralgia
Common	Myalgia, bone pain <sup>1</sup> , osteoporosis, bone fractures, arthritis
Uncommon	Tendonitis
Rare	Tendon rupture
Not known	Trigger finger

**Renal and urinary disorders**

Uncommon	Pollakiuria
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**Reproductive system and breast disorders**

Common	Vaginal haemorrhage
Unknown	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

<sup>1</sup> Adverse drug reactions reported only in the metastatic indication

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 hyperpasia / 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 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%**
Hypercholesterolemia	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 (with a 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 ischemic 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 ischemic attack \* (1.5% vs. 0.8%) were reported.

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

### *Skeletal adverse reactions*

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

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 authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

## **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.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Endocrine therapy. Hormone antagonists and related agents: aromatase inhibitor; ATC code: L02BG04.

### Pharmacodynamic effects

The elimination of estrogen-mediated growth stimulation is a prerequisite for tumor response in cases where the growth of tumor tissue depends on the presence of estrogen and endocrine therapy is used. In postmenopausal women, estrogen are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens - primarily androstenedione and testosterone - to estrone and estradiol. The suppression of estrogen 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 haem of the aromatase cytochrome P450, resulting in a reduction of estrogen 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 estrone and estradiol 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 estradiol, estrone, and estrone sulfate by 75 - 95% from baseline in all patients treated. With doses of 0.5 mg and higher, many values of estrone and estrone sulfate were below the limit of detection in the assays, indicating that higher estrogen suppression is achieved with these doses. Estrogen suppression was maintained throughout treatment in all these patients.

Letrozole is a 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, glucocorticoids and mineralocorticoids 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 estrogen 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 multicenter, double-blind study in which over 8,000 postmenopausal women with hormone receptor positive early breast cancer were randomized 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 of 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						
Medium follow-up 26 months			Medium follow-up 60 months			
Letrozole	Tamoxifen	HR <sup>1</sup>	Letrozole	Tamoxifen	HR <sup>1</sup>	
N = 4003	N = 4007	(95% CI)	N = 4003	N = 4007	(95% CI)	
		P			P	
Disease-free survival (primary) - events (protocol definition <sup>2</sup> )	351	428	0.81 (0.70, 0.93)	585	664	0.86 (0.77, 0.96)
Overall survival (secondary)	166	192	0.86 (0.70, 1.06)	330	374	0.87 (0.75, 1.01)
Number of deaths						

HR = Hazard ratio; CI = Confidence interval

<sup>1</sup> Log rank test, stratified by randomization option and use of chemotherapy (yes/no)

<sup>2</sup> DFS events: loco-regional recurrence, distant metastasis, invasive contralateral breast cancer, second (non-breast) 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 <sup>1</sup> (95% CI)	P-Value
Disease-free survival events (primary) <sup>2</sup>	626	698	0.87 (0.78; 0.97)	0.01
Time to a 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 <sup>3</sup>	626	649	0.83 (0.74; 0.92)	
Censored analysis of OS <sup>3</sup>	393	419	0.81 (0.70; 0.93)	

<sup>1</sup> Log rank test, stratified by randomization option and use of chemotherapy (yes/no)

<sup>2</sup> 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.

<sup>3</sup> Observations in the tamoxifen arm censored at the date of selectively switching to letrozole

*Sequential Treatment 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 significant differences in DFS, OS, SDFS, or DDFS from switch with respect to monotherapy (Table 6).

**Table 6**

Sequential Treatment Analysis of disease-free survival with letrozole as initial endocrine agent (STA switch population)

	N	Number of events <sup>1</sup>	Hazard ratio <sup>2</sup>	(97.5% confidence interval)	Cox model P-value
Letrozole → Tamoxifen	1460	254	1.03	(0.84; 1.26)	0.72
Letrozole	1464	249			

<sup>1</sup> Protocol definition, including second non-breast malignancies, after switching/ beyond two years

<sup>2</sup> Adjusted by chemotherapy use

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

**Table 7**

Sequential Treatments Analysis from the randomization (STA-R) of disease-free survival (IIT STA-R population)

	Letrozole → Tamoxifen	Letrozole
Number of patients	1540	1546
Number of patients with DFS events (protocol definition)	330	319
Hazard ratio <sup>1</sup> (99% CI)	1.04 (0.85; 1.27)	
	Letrozole → Tamoxifen	Tamoxifen <sup>2</sup>
Number of patients	1540	1548
Number of patients with DFS events (protocol definition)	330	353
Hazard ratio <sup>1</sup> (99% CI)	0.92 (0.75; 1.12)	
<sup>1</sup> Adjusted by chemotherapy use (yes/no)		
<sup>2</sup> 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 patients were assigned either letrozole for 5 years or to 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 of lumbar spine but less pronounced.

There was no significant difference between treatments in the rate of fracture – 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 randomized to either letrozole or placebo for 5 years.

The primary endpoint was disease-free survival, defined as the interval between randomization 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 favor of letrozole was observed regardless of node 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 <sup>1</sup>			Median follow-up 62 months <sup>1</sup>		
	Letrozole N=2582	Placebo N=2586	HR (95% CI) <sup>2</sup> <i>P</i> value	Letrozole N=2582	Placebo N=2586	HR (95% CI) <sup>2</sup> <i>P</i> value
<b>Disease free survival<sup>3</sup></b>						
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-years DFS rate	94.4%	89.8%		94.4%	91.4%	
<b>Disease-free survival<sup>3</sup>, including deaths from any cause</b>						
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-years DFS rate	90.5%	80.8%		88.8%	86.7%	
<b>Distant metastases</b>						
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)
<b>Overall survival</b>						
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 <sup>4</sup>	--	--	--	236 <sup>5</sup> (9.1%)	170 <sup>6</sup> (6.6%)	0.78 (0.64, 0.96)

HR = Hazard ratio; CI = Confidence interval

<sup>1</sup> When the study was unblinded in 2003, 1,551 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.

<sup>2</sup> Stratified by receptor status, nodal status and prior adjuvant chemotherapy.



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

<sup>4</sup> Exploratory analysis, censoring follow-up time at the date of switch (if it occurred) in the placebo arm.

<sup>5</sup> Median follow-up 62 months.

<sup>6</sup> Median follow up until switch (if it occurred) 37 months.

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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 estrogen 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 favor 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 the patients had tumors 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 the patients treated with letrozole and 17% of the patients treated with tamoxifen had disease progression on clinical assessment.

### First-line treatment

A 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. In 907 women, letrozole was superior to tamoxifen in time to progression (primary endpoint) and in overall objective response, time to treatment failure and clinical benefit.

The results are summarized in table 9:

**Table 9**

Results at a median follow-up of 32 months

Variable	Statistic	Letrozole	Tamoxifen
		N = 453	N = 454
<b>Time to progression</b>	Median	9.4 months	6.0 months
	(95% CI for the median)	(8.9, 11.6 months)	(5.4, 6.3 months)
	Hazard risk (HR)		0.72
	(95% CI for HR)		(0.62, 0.83)
	<i>P</i>		< 0.0001
<b>Objective response rate (ORR)</b>	CP+PR	145 (32%)	95 (21%)
	(95% CI by 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 antiestrogens has 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 a median of 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 of tamoxifen (logrank test  $P=0.53$ , not significant).

The absence 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 and previously treated with antiestrogens.

Time to progression was not significantly different between letrozole 2.5 mg and megestrol acetate ( $P=0.07$ ). Statistically significant differences were observed in favor of letrozole 2.5 mg compared to megestrol acetate in overall objective tumor 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  $C_{max}$   $129 \pm 20.3$  nmol/l fasted versus  $98.7 \pm 18.6$  nmol/l fed) but the extent of absorption (AUC) is not changed. This 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 proteins 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 of  $^{14}C$ -labeled 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  $1.87 \pm 0.47$  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 fecal excretion play only a minor role in the overall elimination of letrozole. Within 2 weeks after administration of 2.5 mg of  $^{14}C$ -labeled 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 the 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 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 9-116 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 (Study AR/BC2 and Study AR/BC3). Calculated creatinine clearance (CLcr) [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<sub>min</sub>). 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 CLcr or an impairment of renal function.

Therefore, no dose adjustment is required for patient with renal impairment (CLcr  $\geq$ 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 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 the t<sub>1/2</sub> 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 patients.

### **5.3 Preclinical safety data**

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

Letrozole showed a low degree of acute toxicity in rodents exposed up to 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.

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

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

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

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

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

Preclinical observations were confined to those associated with the recognized 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, Carboxymethylstarch sodium (type A) (from potato starch), Microcrystalline cellulose, Hypromellose, Colloidal anhydrous silica and Magnesium stearate.

Coating: Yellow Opadry consisting of: Hypromellose, Macrogol 6000, Titanium dioxide (E171), Yellow iron oxide (E172), Red iron oxide (E172) and tartrazine (E102).

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

Do not store above 30°C. Store in the original package

#### **6.5 Nature and contents of container**

PVC-PVDC / Aluminum blister.

Pack sizes: 30 tablets in a blister pack.

#### **6.6 Special precautions for disposal**

None special.

The elimination of the unused medication and of all the materials that have been in contact with it, will be carried out in accordance with local regulations.

### **7. MARKETING AUTHORISATION HOLDER**

*Imported and distributed by*

Pacific Healthcare (Thailand) Co., Ltd.

1011 Supalai Grand Tower, Room no.01, 29<sup>th</sup> floor,

Rama 3 Road, Chongnonsee, Yannawa, Bangkok, 10120, Thailand.

*Manufactured by*

SAG Manufacturing S.L.U. Crta, N-1 Km 36,

San Agustín de Guadalix, 28750,

Madrid, Spain

### **8. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

### **9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION**

[To be completed nationally]

### **10. DATE OF REVISE OF THE TEXT**

16 Dec 2021