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

Letrozole is not indicated in hormone receptor negative disease.

Letrozole is indicated in:

- Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.

- Extended adjuvant treatment of invasive early breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy for five years.

- First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer.

- Treatment of advanced breast cancer after relapse or progression of the disease in women with natural or artificially induced postmenopausal endocrine state, who have been previously treated with anti-estrogens.

4.2. Posology and method of administration

Adult

The recommended dose of letrozole is 2.5 mg once daily. In the adjuvant and extended adjuvant setting, treatment with Letrovitae should continue for 5 years or until disease relapse/recurrence, whichever comes first.

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

Special populations

Paediatric population

The use of Letrovitae in children and adolescents is not recommended. The safety and efficacy of Letrovitae in children and adolescents up to 17 years of age have not been established. Limited data are available and a dosage recommendation can not be made.

Geriatric patients (65 years of age or older)
No dose adjustment is required for elderly patients.

Renal impairment
No dose adjustment of Letrovitae is required for patients with renal insufficiency with a creatinine clearance ($Cl_{cr)} \geq 10$ ml / min. Sufficient data are not available for cases of renal insufficiency with a creatinine clearance below 10 ml / min (see sections 4.4 and 5.2).

Patients with hepatic impairment
No dose adjustment of letrovitae is required in patients with mild to moderate hepatic impairment (ChildPugh A or B). There is not enough data available on patients with severe hepatic impairment. Patients with severe hepatic impairment (Child-Pugh C) need close monitoring (see sections 4.4 and 5.2)

Method of administration
Letrozole should be taken orally and can be taken with or without food because food has no effect on the extent of absorption.

Missed dose
The missed dose should be taken as soon as the patient remembers. However, if it is almost time for the next dose, 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 CLINICAL PHARMACOLOGY).

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients included in section 6.1.
- Premenopausal endocrine status
- Pregnancy (see section 4.6)
- Lactation (see section 4.6).

4.4. Special warnings and precautions for use

Menopausal state
In patients in whom the state is not clear
postmenopausal, levels of luteinizing hormone (LH), follicle stimulating hormone (FSH) and / or estradiol should be evaluated before starting treatment with letrovitae. Only women in the postmenopausal endocrine state should receive treatment with letrozole.

Renal insufficiency
Letrozole has not been investigated in a sufficient number of patients with creatinine clearance below 10ml / min. The benefit-risk relationship for these patients should be carefully considered before the administration of letrozole.

Hepatic impairment

In patients with severe hepatic impairment (Child-Pugh grade C), the exposure and terminal half-life were approximately twice those observed in healthy volunteers. These patients should be kept under close supervision (see section 5.2).

Bone effects
Letrozole is a potent agent that decreases estrogen. Women with a history of osteoporosis and / or fractures or with an increased risk of osteoporosis should undergo a formal evaluation of bone mineral density before starting adjuvant and adjuvant continuation treatment, and controlled during and after treatment with letrozole. The treatment or prophylaxis of osteoporosis should be initiated when appropriate and carefully controlled. In adjuvant treatment, a sequential treatment regimen (letrozole 2 years followed by tamoxifen 3 years) may also be considered depending on the patient's safety profile (see sections 4.2, 4.8 and 5.1).

Other warnings
The concomitant administration of letrozole with tamoxifen, other antiestrogens or estrogen-containing treatments should be avoided as these substances may decrease 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

The metabolism of letrozole is mainly metabolized in the liver and the cytochrome P450 enzymes CYP2A6 and CYP3A4 mediate the metabolic clearance of letrozole. Therefore, the systemic elimination of letrozole may be influenced by drugs known to affect the CYP3A4 and CYP2A6

Drugs that may increase Letrozole serum concentrations
Inhibitors of CYP3A4 and CYP2A6 activities could decrease the metabolism of letrozole and thereby increase plasma concentrations of letrozole. The concomitant administration of medications that strongly inhibit these enzymes (strong CYP3A4 inhibitors: including but not limited to ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, and telithromycin; CYP2A6 (e.g. methoxsalen) may increase exposure to letrozole. Therefore caution is recommended in patients for whom strong CYP3A4 and CYP2A6 inhibitors are administered.

Drugs that may decrease Letrozole serum concentrations
Inducers of CYP3A4 activity could increase the metabolism of letrozole and thereby decrease plasma concentrations of letrozole. The concomitant administration of medications that induce CYP3A4 (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital, and St. John's Wort) may reduce exposure to letrozole. Therefore, caution is recommended in patients for whom strong CYP3A4 inducers are administered. No drug inducer is known for CYP2A6.

Co-administration of Letrozol (2.5mg) and tamoxifen 20 mg daily resulted in a reduction of letrozole plasma levels by 38% on average. There is limited clinical experience to date on the use of Letrozol in combination with other anti-cancer agents other than tamoxifen.

Drugs that may have their systemic serum concentrations altered by Letrozole
In vitro, letrozole inhibits the cytochrome P450 isoenzymes CYP2A6 and, moderately, CYP2C19, but the clinical relevance is unknown. Caution is therefore indicated when giving letrozole concomitantly with medicinal products whose elimination is mainly dependent on CYP2C19 and whose therapeutic index is narrow (e.g. phenytoin, clopidogrel). No substrate with a narrow therapeutic index is known for CYP2A6.

Clinical interaction studies with cimetidine (a known non-specific inhibitor of CYP2C19 and CYP3A4 and warfarin (sensitive substrate for CYP2C9 with a narrow therapeutic window and commonly used as co-medication in the target population of letrozole) indicated that the coadministration of Letrozol 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.

4.6. Fertility, pregnancy and lactation

Women in a perimenopausal state or in a childbearing age
Only women with a clearly established postmenopausal status should use letrovitae (see section 4.4). Since there are reports of women recovering ovarian function during letrozole treatment despite having a clear postmenopausal state at the start of treatment, the physician should discuss the need for adequate contraception if necessary.

Pregnancy
The human experience in which isolated cases of birth defects have appeared (lip fusion, genital ambiguity) suggests that letrovitae can cause congenital malformations when administered during pregnancy. Studies in animals have shown toxicity to reproduction (see section 5.3).
Letrozole is contraindicated during pregnancy (see sections 4.3 and 5.3).

Lactation
It is not known if letrozole and its metabolites are excreted in breast milk. The risk in newborns / infants can not be excluded.

Letrozole is contraindicated during lactation (see section 4.3).

Fertility

The pharmacological action of letrozole is to reduce the production of estrogen by inhibiting aromatase.

In premenopausal women, the inhibition of estrogen synthesis involves increases in gonadotropin (LH, FSH) levels. Increased levels of FSH in turn stimulate follicular growth and can induce ovulation.

4.7. Effects on ability to drive and use machines

The influence of letrozole on the ability to drive and use machines is small.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 frequency of adverse reactions for letrozole is mainly based on data collected from clinical trials.

Up to approximately one third of the patients treated with letrozole in the metastatic indication and approximately 80% of the patients in the adjuvant indication, as well as in the adjuvant continuation indication presented adverse reactions. Most adverse reactions appeared during the first weeks of treatment.

The most frequent adverse reactions observed in the clinical trials were hot flushes, hypercholesterolemia, arthralgia, fatigue, increased sweating and nausea.

Other important adverse reactions that can appear with letrozole are: bone events such as osteoporosis and / or bone fractures and cardiovascular events (including cerebrovascular and thromboembolic events). The frequency category of these adverse reactions is described in Table 1.

Tabular list of adverse reactions

The frequency of adverse reactions for letrozole is mainly based on data collected from clinical trials.

In the clinical trials and in the post-marketing experience of letrozole, the adverse reactions listed below were recorded in Table 1:

Table 1

Adverse reactions are classified by frequencies, first the most frequent, using the following convention: very common ≥ 10%, common ≥ 1% to <10%, uncommon ≥ 0.1% to <1%, rare ≥ 0.01 % to <0.1%, very rare <0.01%, not known (can not 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	Leucopenia
Immune system disorders	
Not known	Anaphylactic reaction
Metabolism and nutrition disorders	
Very common	Hypercolesterolemia
Common	Anorexia, appetite increase.
Sychiatric disorders	
Common	Depression
Uncommon	Anxiety (including nervousness), irritability
Nervous system disorders	
Common	Headache, dizziness
Uncommon	Somnolence, insomnia, memory impairment, dysaesthesia (including paresthesia), taste disturbance, cerebrovascular accident
Eye disorders	
Uncommon	Cataract, eye irritation, blurred vision
Cardiac disorders	
Uncommon	Tachycardia, cardiac ischemic events (including new onset angina or worsening, angina requiring surgery, myocardial infaction and myocardial ischemia)
Common	Palpitations[1]
Vascular disorders	
Very common	Hot flushes
Common	Hypertension
Uncommon	Thrombophlebitis (including superficial and deep vein thrombophlebilits)
Rare	Pulmonary embolism, arterial thrombosis, cerebrovascular infarction
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, cough
Gastrointestinal disorders	
Common	Nausea, dyspepsia[1], constipation, abdominal pain, diarrhoea, vomiting
Uncommon	Stomatitis[1], dry mouth
Hepatobiliary disorders	
Uncommon	Increased hepatic enzymes, hyperbilirubinemia, jaundice
Common	Hepatitis
Skin and subcutaneous tissue disorders	
Very common	Increased sweating,
Common	Alopecia, rash (including erythematous, maculopapular rash, psoriaforme and vesicular), 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
Renal and urinary disorders	
Uncommon	Increased urinary frequency

Reproductive system and breast disorders	
Common	Vaginal bleeding
Unknown	Vaginal discharge, vaginal dryness, breast pain
General disorders and administration site conditions	
Very common	Fatigue (including asthenia, malaise)
Common	Peripheral oedema, chest pain
Uncommon	General oedema, dry mucous membranes, thirst, pyrexia
Investigations	
Common	Weight increase
Uncommon	Weight loss

[1] Adverse reactions reported only in the metastatic indication

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

Table 2 Adjuvant monotherapy of letrozole versus monotherapy with tamoxifen - adverse reactions with significant differences

	Letrozol, incidence rate	**Tamoxifeno, incidence rate**
bone bill	10.11% (13.8%)	7.1% (10.5%)
osteoporosis	5.1% (5.1%)	2.7% (2.7%)
thromboembolic events	2.1% (2.9%)	3.6% (4.5%)
myocardial infarction	1.0% (1.5%)	0.5% (1.0%)
endometrial hyperpasia / endometrial cancer	0.2% (0.4%)	2.3% (2.9%)
Note: Median duration of treatment 60 months. The notification period includes the treatment period plus 30 days after the end of treatment. The percentages in parentheses indicate the frequencies of the events at any time after randomization, including the post-study treatment period. The median follow-up was 73 months.		

Table 3 Sequential treatment versus monotherapy with letrozole - adverse reactions with significant differences

	Letrozole, monotherapy	**Tamoxifen → Letrozole**	**Letrozole → Tamoxifen**
bone bill	9.9%	7.6%*	9.6%
proliferative disorders of the endometrium	0.7%	3.4%**	1.7%**
hypercholesterolemia	52.7%	44.2%*	40.8%*
hot flushes	37.7%	41.7%**	43.9%**
vaginal bleeding	6.3%	9.6%**	12.7%**
* Significantly lower than with monotherapy with letrozole ** Significantly greater than with monotherapy with letrozole Note: The notification period is during the treatment or within 30 days after the end of treatment			

Description of the selected adverse reactions

Cardiac adverse reactions

In the adjuvant indication, in addition to the data presented in Table 2, the following adverse reactions were reported for letrozole and tamoxifen, respectively (with a median treatment duration of 60 months plus 30 days): angina requiring surgery (1, 0% versus 1.0%); heart failure (1.1% versus 0.6%); hypertension (5.6% versus 5.7%); cerebrovascular accident / transient ischemic attack (2.1% versus 1.9%).

Follow-up adjuvant indication was reported for letrozole (median duration of treatment 5 years) and for placebo (median duration of treatment 3 years), respectively: angina requiring surgery (0.8% vs. 0.6%) ; New onset or worsening angina (1.4% vs. 1.0%); myocardial infarction (1.0% versus 0.7%); thromboembolic event * (0.9% vs. 0.3%); cerebrovascular accident / transient ischemic attack * (1.5% vs. 0.8%).

The events marked with * were different in a statistically significant way in the two treatment arms.

Adverse bone reactions

To consult the bone safety data of the adjuvant indication, see Table 2.

In the follow-up adjuvant indication, significantly more patients treated with letrozole had bone fractures or osteoporosis (bone fractures, 10.4% and osteoporosis, 12.2%) compared with patients in the placebo arm (5.8% and 6.4%, respectively). The median duration of treatment was 5 years for letrozole versus 3 years for placebo.

Notification of suspected adverse reactions:

It is important to report suspected adverse reactions to the medication after authorization. This allows a continuous monitoring of the benefit / risk ratio of the medicine.

4.9. Overdose

Isolated cases of overdose with letrozole have been reported

There is no known specific treatment for overdose; the treatment must be symptomatic and supportive.

5. PHARMACOLOGIACAL PROPERTIES

5.1. Pharmacodynamic properties

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

Pharmacodynamic effects

In endocrine therapy, the elimination of estrogen-mediated growth stimulation is a prerequisite for tumor response in those cases in which the growth of tumor tissue depends on the presence of estrogen. In postmenopausal women, estrogen comes mainly from the action of the aromatase enzyme, which converts androgens - mainly androstenedione and testosterone - into estrone and estradiol.

The suppression of estrogen biosynthesis in the peripheral tissues and in the neoplastic tissue itself can therefore be achieved by a specific inhibition of the aromatase enzyme.

Letrozole is a non-steroidal aromatase inhibitor. It inhibits aromatase enzyme by competitive binding of cytochrome P450 aromatase hemoglobin, resulting in a reduction of estrogen synthesis in all tissues where it is present.

In healthy postmenopausal women, single doses of 0.1 mg, 0.5 mg and 2.5 mg of letrozole suppress serum estrone and estradiol in 75%, 78% and 78% of basal levels, respectively. The maximum suppression was reached in 48-78 hours.
In postmenopausal patients with advanced breast cancer, daily doses of 0.1 mg to 5 mg suppress the plasma concentration of estradiol, estrone, and estrone sulfate in 75% -95% of baseline levels in all treated patients. At doses of 0.5 mg and above, many of the values of estrone and estrone sulfate are below the limit of detection in the trials, indicating that a greater estrogenic suppression is achieved with these doses. The estrogenic suppression was maintained throughout the treatment in all patients.

Letrozole is a highly specific inhibitor of aromatase activity. No deterioration of adrenal steroidogenesis was observed. No clinically relevant changes were found in the plasma levels of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxyprogesterone and ACTH, nor in the activity of plasma renin, in postmenopausal women treated with a daily dose of between 0.1 to 5 mg of letrozole. The ACTH stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 2.5 mg and 5 mg showed no decrease in production of aldosterone or cortisol. Therefore, a supplemental addition of glucocorticoids and mineralocorticoids is not necessary.

No changes were observed in plasma androgen concentrations (androstenedione and testosterone) in healthy postmenopausal women treated with single doses of 0.1 mg, 0.5 mg and 2.5 mg of letrozole nor in plasma concentrations of androstenedione in patients postmenopausal women treated with daily doses of 0.1 to 5 mg of letrozole, indicating that the blockade of estrogen synthesis does not produce accumulation of androgenic precursors. Plasma levels of LH and FSH and thyroid function assessed by TSH, T4 and T3 uptake were not affected by letrozole.

Adjuvant treatment
Study BIG 1-98
The BIG 1-98 trial was a multicenter, double-blind study; more than 8,000 postmenopausal women with early breast cancer with a positive hormone receptor 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 main variable was disease-free survival (DFS); secondary efficacy variables 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 the recurrence of breast cancer.

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

The data in Table 4 reflect the results of the Primary Core Analysis based on the data of the arms with monotherapy (A and B) and the data of the two arms of change of treatment (C and D) to an average duration of treatment of 24 months and a median follow-up of 26 months and a median duration of treatment 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 survival and overall survival, at a median follow-up of 26 months and a median follow-up of 60 months (IT population - intention to treat)

	Primary Central Analysis					
	Medium follow-up 26 months			**Medium follow-up 60 months**		
	Letrozole N = 4.003	**Tamoxifen N = 4.007**	**HR[1] (IC 95%) *P***	**Letrozole N = 4.003**	**Tamoxifen N = 4.007**	**HR[1] (IC 95%) *P***
Disease-free survival (primary) - events (definition by protocol)[2]	351	428	0.81 (0.70; 0.93; 0.003)	585	664	0.86 (0.77; 0.96; 0.008)
Global survival (secondary) Number of deaths	166	192	0.86 (0.70; 1.06)	330	374	0.87 (0.75; 1.01)

HR = Hazard ratio; IC = Confidence interval

[1] Test of Logrank, stratified by randomization option and use of chemotherapy (yes/no).

[2] DFS events: loco-regional recurrence, distant metastasis, invasive contralateral breast cancer, second primary malignant processes (not mammary), death from any cause without a previous cancer event.

[3] Number of deaths

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

Table 5 shows the Monotherapy Arms Analysis (ABM), long-term update of the efficacy of letrozole monotherapy compared to tamoxifen monotherapy (median duration of adjuvant treatment: 5 years).

Table 5 Analysis of monotherapy arms: disease-free survival and overall survival with a median follow-up of 96 months (IT population)

	Letrozole N = 2463	**Tamoxifen N = 2459**	**Hazard Ratio[1] (IC 95)**	**Valor *P***
Disease-free survival events[2]	626	698	0.87 (0.78;0.97)	0.01
Time to a distant metastasis	301	342	0.86 (0.74; 1.01)	0.06
Overall survival [3]	393	436	0.89 (0.77, 1.02)	0.08
Censored analysis of DFS[4]	626	649	0.83 (0.74; 0.92)	
Censored analysis of OS[4]	393	419	0.81 (0.70; 0.93)	

[1] Logrank test, stratified by randomization option and use of chemotherapy (yes / no)
[2] DFS events: loco-regional recurrence, distant metastasis, invasive contralateral breast cancer, second primary malignant processes (not mammary), death from any cause without a previous event of cancer.
[3] Number of deaths
[3] Observations in the tamoxifen arm censored at the date of selectively switching to letrozole after tamoxifen arm was unblinded

Sequential Treatment Analysis (STA)
The Analysis of Sequential Treatments (STA) addresses the second main issue of BIG 1-98, that is, if the sequencing of tamoxifen and letrozole treatments would be superior to monotherapy. No significant differences were observed in the DFS, OS, SDFS, or DDFS of the change with respect to monotherapy (Table 6).

Table 6 Sequential treatment analysis of disease-free survival with letrozole as the initial endocrine agent (STA population of the change)

	N	**Number of events[1]**	**Hazard ratio[2]**	**(Confidence interval 97.5%)**	**Cox model value *P***
Letrozole → Tamoxifen	1.460	254	1.03	(0.84; 1.26)	0.72
Letrozole	1.463	249			

[1] Definition of protocol, including second primary non-breast malignancies, after the change / beyond two years
[2] Adjusted for the use of chemotherapy

No significant differences were observed in DFS, OS, SDFS, DDFS in any of the ATS since randomization in paired comparisons (Table 7).

Table 7 Analysis of sequential treatments from the randomization (STA-R) of disease-free survival (IT population STA-R)

	Letrozole→ Tamoxifen	**Letrozol**
Number of patients	1.540	1.546
Number of patients with DFS events (definition of the protocol)	330	319
Hazard ratio[1] (IC 99%)	1.04 (0.85; 1.27)	
	Letrozole→ Tamoxifen	**Tamoxifeno[2]**
Number of patients	1.540	1.548
Number of patients with DFS events (definition of the protocol)	330	353
Hazard ratio[1] (IC 99%)	0.92 (0.75; 1.12)	
[1] Adjusted for the use of chemotherapy [2] 624 (40%) patients crossed selectivity to letrozole after opening the cecum in the tamoxifen arm in 2005.		

The following tables 8 and table 9 provide information on significant differences in Letrozol versus tamoxifen monotherapy and in the Letrozol-tamoxifen sequential treatment therapy:

Table 8 Adjuvant Letrozol monotherapy versus tamoxifen monotherapy – adverse events with significant differences

	Letrozol N=2448		**Tamoxifen N=2447**	
	During treatment (median 5 years)	**Any time after randomization (median 96 months)**	**During treatment (median 5 years)**	**Any time after randomization (median 96 months)**
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: Median duration of treatment 60 months. Reporting period includes treatment period plus 30 days after stopping treatment. ”Any time after randomization” includes the follow-up period after completion or cessation of study treatment				

Table 9 Sequential treatment versus Letrozol monotherapy – adverse events with significant differences

	Letrozol monotherapy 5 years	**Letrozol >Tamoxifen 2 years + 3 years**	**Tamoxifen >Letrozol 2 years + 3 years**
	N=1535	**N=1527**	**N=1541**
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 Letrozol monotherapy **Significantly more than with Letrozol monotherapy Note : Reporting period is during treatment or within 30 days of stopping treatment			

Study CFEM345D2407

The trial D2407 is an open-label, randomized, multicentre, post authorization study designed as a safety study to compare the adjuvant treatment with letrozole and tamoxifen about bone mineral density (BMD) and serum lipid profiles. A total of 263 patients were assigned to letrozole during 5 years (133 postmenopausal women) or to tamoxifen during 2 years followed by letrozole during 3 years (130 patients).

At 24 months a statistically significant difference was observed in the main variable. The BMD of the lumbar spine (L2-L4) showed a decrease median of 4.1% for letrozole compared to an increase median of 0.3% for tamoxifen. The results for total hip BMD were similar to those for lumbar spine but less pronounced.

No patient with a normal BMD at baseline became osteoporotic during 5 years of treatment. One patient with osteopenia at baseline (T-score of -1.9) developed osteoporosis during the treatment period (assessment by central review).

Although treatment differences at the end of 5 years were attenuated such that there was no statistically significant difference between treatments in the protocol-defined clinically relevant BMD-related changes overall, there remained substantial differences in the effects of the two treatments on BMD and skeletal events. In patients with a normal T-score at baseline, significantly more patients in the letrozole arm than in the sequential treatment arm had reductions of at least 6% in lumbar spine BMD within 1 year or cumulative reductions of at least 8% over the entire treatment period. Although there was no significant difference overall between treatment arms in clinical fractures, three-quarters of the fractures in the sequential treatment arm occurred after the switch to letrozole. Both clinical fractures and impending fractures, however, tended to occur in patients whose skeletal status was compromised – i.e. patients with lower BMD T-scores at baseline, and patients with a history of fractures.

Total cholesterol levels (fasting) decreased by a median 16% in the tamoxifen arm at 6 months, and remained so for the duration of tamoxifen therapy. In the letrozole arm, total cholesterol levels were relatively stable throughout treatment. LDL cholesterol levels decreased in the tamoxifen arm but remained stable in the letrozole arm. Consequently, there were statistically significant differences in favour of tamoxifen in total cholesterol, LDL cholesterol and HDL: LDL ratio over the first 2 years of the study. There were no significant differences between treatments in triglycerides.

Extended adjuvant treatment
Study MA-17 (CFEM345MA17)

In a multicentre, double-blind, randomized, placebo-controlled study (MA-17), conducted in more than 5,100 postmenopausal patients with primary breast cancer with positive or unknown receptor, who had completed adjuvant treatment with tamoxifen (4.5 a 6 years) were randomized to letrozole or placebo for 5 years.

The primary variable was disease-free survival, defined as the time from randomization to the event that appears before: loco-regional recurrence, distant metastasis, or contralateral breast cancer.

The first planned intermediate analysis at a median follow-up of about 28 months (25% of patients followed up to at least 38 months), showed that letrozole significantly reduced the risk of recurrence of breast cancer by 42% compared to placebo (HR 0.58; 95% CI 0.45, 0.76, P = 0.00003). The benefit in favor of

letrozole was observed independently of the lymph 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 intermediate analysis the randomization code was opened and the study continued openly and patients in the placebo arm were able to switch to letrozole for up to 5 years. Sixty percent of patients who were candidates for change (disease-free at the time of the open-label study) chose to switch to letrozole. The final analysis included 1,551 women who went from placebo to letrozole for a median of 31 months (range 12 to 106 months) after completing adjuvant therapy with tamoxifen. The median duration for letrozole after the change was 40 months.

The final analysis performed with a median follow-up of 62 months confirmed the significant reduction in the risk of recurrence of breast cancer with letrozole.

Table 10 Disease-free survival and overall survival (Modified IT population)

	Median follow-up 28 months			Median follow-up 62 months[1]		
	Letrozole N=2.582	Placebo N=2.586	HR (IC 95%)[2] Valor *P*	Letrozole N=2.582	Placebo N=2.586	HR (IC 95%)[2] Valor *P*
Disease free survival[3]						
Events	92 (3.6%)	155 (6.0%)	0.58 (0.45; 0.76) 0.00003	209 (8.1%)	286 (11.1%)	0.75 (0.63; 0.89)
DFS Rate at 4 years	94.4%	89.9%		94.4%	91.4%	
Disease free survival[3], including any cause deaths						
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)
DFS Rate at 5 years	90.5%	80.8%		88.8%	86.7%	
Distant metastasis						
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)
Global 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 randomization code of the study was opened in 2003, 1,551 patients assigned to the placebo arm switched to letrozole (60% of whom were candidates for change - ie they were free of disease) at a median of 30 months after randomization. The analyses presented here do not take into account selective crossover.

[2] Stratified by recipient status, lymph node status and previous adjuvant chemotherapy.

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

[4] Exploratory analysis, follow-up time censored at the date of the change (if it occurred) in the placebo arm.

[5] Median follow-up of 62 months.

[6] Median follow up until the change (if it happened) 37 months.

In the bone substudy of MA-17 in which calcium and vitamin D were administered concomitantly, greater decreases in BMD were observed with respect to the baseline value with letrozole than with placebo. The only statistically significant difference was observed at 2 years and it was in the total BMD of the hip (median decrease with letrozole of 3.8% versus median decrease with placebo of 2.0%).

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

In the updated quality of life substudy no significant differences were observed between treatments in the summary scores of the physical component or summary scores of the mental component, or in any score of the domain of the SF-36 scale. On the MENQOL scale, significantly more women in the letrozole arm than in the placebo arm were more concerned (usually in the first year of treatment) for these symptoms derived from estrogen deprivation - hot flushes and vaginal dryness. The symptom that worried most patients in both treatment arms was muscle pain, with a statistically significant difference in favor of placebo.

Neoadjuvant treatment

A double-blind trial (P024) was conducted in 337 postmenopausal patients with breast cancer randomized either to letrozole 2.5 mg for 4 months or to tamoxifen for 4 months. In the beginning, all the patients presented tumors in a T2-T4c, N0-2, M0, ER and / or PgR positive state and none of the patients would have been eligible for breast-conserving surgery. Based on the clinical assessment, 55% of objective responses were observed in the letrozole arm compared to 36% for the tamoxifen arm (P <0.001). This result was confirmed consistently by ultrasound (35% letrozole versus 25% tamoxifen, P = 0.04) and mammography (34% letrozole versus 16% tamoxifen, P <0.001). A total of 45% of patients in the letrozole group versus 35% of patients in the tamoxifen group (P = 0.02) had breast-conserving surgery. During the 4-month preoperative treatment period, 12% of the patients treated with letrozole and 17% of the patients treated with tamoxifen had a progression of the disease according to clinical evaluation.

First line treatment

A double-blind, controlled clinical trial was conducted comparing 2.5 mg of letrozole versus 20 mg of tamoxifen as first-line therapy in postmenopausal women with advanced breast cancer.

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

The results are summarized in table 10:

Table 11 Results of a median follow-up of 32 months

Variable	Statistical	Letrozole N = 453	Tamoxifen N = 454
Time to progression	Median	9.4 months	6.0 months
	(IC 95% for the median)	(8.8, 11.6 months)	(5.4, 6.3 months)
	Hazard risk (HR)	0.72	

	(IC 95% for HR)	(0.62; 0.83)	
	P	< 0.0001	
Objective response rate (ORR)	CP+PR	143 (32%)	95 (21%)
	(IC 95% by rate)	(28, 36%)	(17, 25%)
	Odds ratio	1.78	
	(IC 95% for odds ratio)	(1.32; 2.40)	
	P	0.0002	

The time to progression was significantly longer, and the response rate was significantly higher for letrozole regardless of whether adjuvant treatment with antiestrogens was administered or not. The time to progression was significantly longer for letrozole regardless of the predominant location of the disease. The median time to progression was 12.1 months for letrozole and 6.4 months for tamoxifen in patients with only soft tissue disease and a median of 8.3 months for letrozole and 4.6 months for tamoxifen. in patients with visceral metastases.

The design of the study allowed the patients to cross over to the other treatment during the progression or to leave the study. Approximately 50% of the patients switched to the opposite treatment group and the crossing was completed in virtually 36 months. The median time to crossing was 17 months (from letrozole to tamoxifen) and 13 months (from tamoxifen to letrozole).

Therapy with letrozole in the first-line treatment of advanced breast cancer resulted in a median overall survival of 34 months compared to 30 months of tamoxifen (log rank test P = 0.53, not significant). The absence of letrozole advantage over total survival could be explained by the cross-sectional design of the study.

Second line treatment
Two controlled clinical trials were conducted comparing two doses of letrozole (0.5 mg and 2.5 mg) with megestrol acetate and aminoglutethimide, respectively, in postmenopausal women with advanced breast cancer and previously treated with antiestrogens.

Study AR/BC2
The period of 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 the overall objective tumor response index (24% vs 16%, P = 0.04), and in the period of time until treatment failure (P = 0.04). Overall survival was not significantly different between the two groups (P = 0.2 and P=0.07, respectively).

In the second study (Study AR/BC3), 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 in terms of time to progression (P = 0.008), time to treatment failure (P = 0.003) and overall survival (P = 0.002).

Breast cancer in men
The 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%). Foods slightly decrease the absorption rate (median tmax: 1 hour fasting versus 2 hours with food, and Cmax average: 129 ± 20.3 nmol / l fasting versus 98.7 ± 18.6 nmol / l with the food), but does not alter the magnitude of absorption (AUC). This minor effect on the rate of absorption is not considered clinically relevant and therefore letrozole can be administered independently of meals

Distribution

Letrozole binds to plasma proteins in approximately 60%, mainly to albumin (55%). The concentration of letrozole in erythrocytes is approximately 80% of the plasma concentration. After administration of 2.5 mg of 14 C-labeled letrozole, approximately 82% of the radioactivity in plasma corresponded to the unchanged compound. The systemic exposure to metabolites is, therefore, low. Letrozole is rapidly and extensively distributed to the tissues. Its apparent volume of distribution at steady state is approximately 1.87 ± 0.47 l / kg.

Biotransformation

Metabolic clearance to a pharmacologically inactive carbinol metabolite is the main route of elimination of letrozole (CL_m = 2.1 l / h) but is relatively slow when compared to the hepatic blood flow (approximately 90 l / h). It was observed that the isoenzymes of cytochrome P450, 3A4 and 2A6 were able to convert letrozole into this metabolite. The formation of less frequent unidentified metabolites and direct renal and fecal excretion play only a minor role in the overall elimination of letrozole. During the 2 weeks following the administration of 2.5 mg of 14C-labeled letrozole to healthy postmenopausal volunteers, 88.2 ± 7.6% of the radioactivity was recovered in urine and 3.8 ± 0.9 in the faeces. %. At least 75% of the radioactivity recovered in the urine in 216 hours (84.7 ± 7.8% of the dose) was attributed to the glucuronide of the metabolite carbinol, approximately 9% to two unidentified metabolites and 6% to unchanged letrozole.

The apparent terminal elimination half-life in plasma is about 2 days. After administration of 2.5 mg daily, steady-state levels are reached in 2-6 weeks. The steady-state plasma concentrations are approximately 7 times higher than the concentrations 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 after a single dose , indicating a slight non-linearity in the pharmacokinetics of letrozole after the daily administration of 2.5 mg. Considering that steady-state levels are maintained over time, it can be concluded that there is no continuous accumulation of letrozole.

Special populations

Elderly patients

Age has no effect on the pharmacokinetics of letrozole.

Renal insufficiency

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

Liver failure
In a similar study with patients with varying degrees of hepatic impairment, mean AUC values of volunteers with moderate hepatic impairment (Child-Pugh grade B) were 37% higher than those of normal subjects, but within the range observed in subjects without functional deterioration. 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 grade C) with pharmacokinetics in healthy volunteers (N = 8), the AUC and the $t_{1/2}$ increased by 95 and 187% respectively. Therefore, letrozole should be administered with caution and after considering the possible risk / benefit in this type of patients.

5.3. Preclinical safety data

In a series of preclinical safety studies carried out with standard animal species, no evidence of systemic or target organ toxicity was found.

Letrozole showed a low degree of acute toxicity in rodents exposed to doses up to 2,000 mg / kg. In dogs, letrozole caused signs of moderate toxicity at a dose of 100 mg / kg. In toxicity studies of up to 12 months with repeated doses in rats and dogs, the main findings observed can be attributed to the pharmacological action of the active substance. The level of no adverse effect was 0.3 mg / kg in both species.

Investigations in vivo and in vitro on the mutagenic potential of letrozole revealed no evidence of genotoxicity.

In a carcinogenicity study of 104 weeks in rats, no treatment-related tumor was observed in male rats. In female rats a low incidence of benign and malignant breast tumors was found with all doses of letrozole.

Letrozole was embryotoxic and fetotoxic in pregnant rats and rabbits after oral administration at clinically relevant doses. In rats had live fetuses, a higher incidence of fetal malformations was observed including vaulted head and fusion of cervical / central vertebrae. There was no increase in the incidence of fetal malformations in rabbits. It is unknown whether this was an indirect consequence of the pharmacological properties (inhibition of estrogen biosynthesis) or a direct effect of the drug (see sections 4.3 and 4.6).
The preclinical observations were limited to those associated with the known pharmacological action that is the only one of interest in human safety 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.

Manufacturer: SAG Manufacturing S.L.U. Ctra. N-I, Km 36, San Agustín de Guadalix, 28750 Madrid - Spain

Product Owner: Galenicum Health S.L., Av. Diagonal 123, 11th floor, 08005, Barcelona – Spain

Product Registrant: United Italian Trading Corporation (Pte) Ltd - 28 Tai Seng Street, #06-01 Sakae Building - Singapore 534106