SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LETRASAN 2.5 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains
Active substance:

Letrozole	2.5 mg

Excipients:

Lactose monohydrate (from cow milk)	64.5 mg
Sodium starch glycolate	4mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.
Yellow, round film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Letrozole is not indicated for hormone receptor negative disease.
Letrozole is indicated for the following conditions:

- Adjuvant treatment of postmenopausal women with hormone receptor (estrogen (ER) and/or progesterone (PR) receptor) positive early breast cancer,
- Postmenopausal, hormone receptor (ER and/or PR receptor) positive, early stage invasive breast cancer patients who have previously used standard (5 years) tamoxifen, in prolonged adjuvant treatment,
- It is indicated as first-line treatment in postmenopausal women with metastatic and local, advanced breast cancer and hormone receptor (ER and/or PR) positive.
- It is also indicated for the treatment of postmenopausal women with breast cancer that has relapsed or progressed after tamoxifen therapy.

4.2 Posology and method of administration

Posology/Frequency and duration of administration
The recommended dose of LETRASAN for adults is 2.5 mg once daily. In the adjuvant and extended adjuvant setting, treatment with LETRASAN should continue for 5 years or until tumor relapse occurs (whichever comes first). In the large pivotal study of letrozole versus tamoxifen in the adjuvant setting, no benefit in efficacy or safety was obtained by sequential administration of these treatments compared with letrozole administered continuously for 5 years. In women with metastatic disease, treatment with LETRASAN should continue until tumor progression is evident.
It should not be used without physician advice. Unless otherwise recommended by the physician, above-mentioned dose is used.

Method of administration
LETRASAN should be taken orally and can be taken with or without food because food has no effect on the extent of absorption.
LETRASAN should be used once daily and preferably at the same time of each day.
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 5.1).

Additional information on special populations

Renal impairment
No dose adjustment of LETRASAN is required for patients with renal impairment with creatinine clearance (CLcr) ≥10 ml/min. Insufficient data are available in cases of renal impairment with CLcr <10 ml/min (see sections 4.4 and 5.2).

Hepatic Impairment
No dose adjustment of LETRASAN is required for patients with mild to moderate hepatic impairment (Child-Pugh score A or B). Insufficient data are available for patients with severe hepatic impairment, but patients with severe hepatic impairment (Child-Pugh score C) should be kept under close supervision (see sections 4.4 and 5.2).

Pediatric population
LETRASAN 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 no recommendation on a posology can be made.

Geriatric population
No dosage adjustment is required for geriatric patients.

4.3 Contraindications
- In patients with hypersensitivity to the active substance letrozole or to any of the other ingredients,
- In women with premenopausal endocrine status
- during pregnancy and breast-feeding (see section 4.6)

4.4 Special warnings and precautions for use

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

Renal impairment
Letrozole has not been investigated in patients with creatinine clearance <10 ml/min. The potential risk/benefit to such patients should be carefully considered before administration of LETRASAN.

Hepatic impairment
In patients with severe hepatic impairment (Child-Pugh score C), systemic exposure and terminal

half-life were approximately doubled compared to healthy volunteers. Such patients should therefore be kept under close supervision (see section 5.2).

Bone effects
LETRASAN 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 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. immobilization) must be initiated for the affected tendon (see section 4.8).

Other warnings
Co-administration of LETRASAN with tamoxifen, other anti-estrogens or estrogen-containing therapies should be avoided as these substances may diminish the pharmacological action of letrozole (see section 4.5).

Excipients
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or of glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol (23 mg) of sodium per tablet, meaning it is essentially "sodium-free."

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, 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 estrogens or other anticancer agents, other than tamoxifen. Tamoxifen, other anti-estrogens 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. Co-administration of letrozole with tamoxifen, other anti-estrogens or estrogens 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, clopidrogel).

Additional information on special populations
No clinical interaction study for special populations has been conducted.

4.6 Pregnancy and lactation

General recommendation
Pregnancy category: X

Women of child-bearing potential/Birth control (Contraception)
LETRASAN 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
LETRASAN is contraindicated during pregnancy (see section 4.3 and section 5.3).

Post-marketing reports have reported spontaneous abortions and congenital anomalies in infants of mothers taking letrozole (see section 4.4). Animal studies have shown reproductive toxicity.

Letrozole has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn. Isolated cases of birth defects (labial fusion, ambiguous genitalia) have been reported in pregnant women exposed to letrozole (see section 5.3).

Breast-feeding
LETRASAN is contraindicated during breastfeeding (see section 4.3). It is unknown whether letrozole is excreted in breast milk. A risk to the newborn/child cannot be excluded.

Reproductive ability/Fertility
The pharmacological action of letrozole is to reduce estrogen production by aromatase inhibition. Inhibition of estrogen synthesis in premenopausal women leads to an increase in gonadotropin (LH, FSH) levels with the opposite effect. Increased FSH levels in turn stimulate follicular growth, and can induce ovulation.

4.7 Effects on ability to drive and use machinery
LETRASAN 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
The frequencies of adverse reactions for letrozole are based primarily on data collected from clinical studies.

Up to one-third of patients treated with letrozole for metastatic disease, and approximately 80% of patients in the adjuvant and extended adjuvant settings, experienced adverse events. The majority of adverse reactions occurred during the first few weeks of treatment.

The most frequently reported adverse reactions in clinical trials were hot flushes, hypercholesterolemia, arthralgia, fatigue, increased sweating, and nausea.

Additional important adverse reactions that may be seen with letrozole include: bone events, such as osteoporosis and/or bone fractures, and cardiovascular events (including cerebrovascular and thromboembolic events). The frequency categories of these adverse reactions are described below.

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥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

Benign and malignant neoplasms (including cysts and polyps):
Uncommon: Tumor pain[1]

Blood and lymphatic system disorders:
Uncommon: Leukopenia

Immune system disorders:
Unknown: Anaphylactic reaction

Metabolism and nutritional disorders:
Very common: Hypercholesterolemia
Common: Increased appetite, decreased appetite

Psychiatric disorders:
Common: Depression
Uncommon: Anxiety (including irritability), irritability

Nervous system disorders:
Common: Headache, dizziness
Uncommon: Somnolence, insomnia, memory impairment, dysesthesia (including paresthesia and hypoesthesia), taste disturbances, cerebrovascular event, carpal tunnel syndrome

Eye diseases:
Uncommon: Cataracts, eye irritation, blurred vision

Cardiac disorders:
Common: Palpitations[1]
Uncommon: Tachycardia, ischemic cardiac events (includes new or worsening angina, angina requiring surgery, myocardial infarction, and myocardial ischemia)

Vascular diseases:
Very common: Hot flashes
Common: Hypertension
Uncommon: Thrombophlebitis (including superficial and deep thrombophlebitis)
Rare: Pulmonary embolism, arterial thrombosis, cerebrovascular infarction

Respiratory, thoracic, and mediastinal disorders:
Uncommon: Dyspnea, cough

Gastrointestinal disorders:
Common: Nausea, vomiting, dyspepsia[1], constipation, diarrhea, abdominal pain
Uncommon: Stomatitis[1], dry mouth

Hepatobiliary disorders:
Uncommon: Elevated liver enzymes, hyperbilirubinemia, jaundice
Very rare: Hepatitis

Skin and subcutaneous tissue disorders:
Very common: Increased sweating
Common: Alopecia, dry skin, rash (including erythematous, maculopapular, psoriasiform, and vesicular rashes)
Uncommon: Pruritus, urticaria
Unknown: Angioedema, toxic epidermal necrolysis, erythema multiforme

Musculoskeletal, connective tissue, and bone disorders:
Very common: Joint pain
Common: Myalgia, bone pain1, osteoporosis, bone fractures, arthritis
Uncommon: Tendonitis
Rare: Tendon rupture
Unknown: Trigger finger

Kidney and urinary tract diseases:
Uncommon: Frequent urination

Reproductive system and breast disorders:
Uncommon: Vaginal bleeding.
Uncommon: Vaginal discharge, vaginal dryness, breast pain.

General disorders and administration site conditions:
Very common: Fatigue (including asthenia and malaise)
Common: Peripheral edema, chest pain
Uncommon: General edema, pyrexia, dry mucosa, thirst feeling

Investigations:
Common: Weight gain
Uncommon: Weight loss

[1] *Adverse drug reactions reported only in the metastatic setting*

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

Table 1 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 2 Sequential treatment versus Letrozole monotherapy – adverse events with significant differences

	Letrozole monotherapy	Letrozole ->tamoxifen	Tamoxifen-> Letrozole
	N=1535	N=1527	N=1541
	5 years	2 yrs-> 3 yrs	2 yrs-> 3 yrs
Bone fractures	10.0%	7.7%*	9.7%
Endometrial proliferative disorders	0.7%	3.4%**	1.7%**
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 (median treatment duration 5 years): 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 with * were statistically significantly different between 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 authorization 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 the national reporting system.

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: Hormone antagonists and related agents: Aromatase inhibitor (inhibitor of estrogen biosynthesis); antineoplastic agent.
ATC code: L02BG04

Mechanism of action:
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 estrogens. In postmenopausal women, estrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens (primarily androstenedione and testosterone) to estrone (E1) and estradiol (E2). 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 the haem of the aromatase cytochrome P450, resulting in a reduction of estrogen biosynthesis in all tissues.

Pharmacodynamics
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 to 5 mg suppress plasma concentration of estradiol, estrone, and estrone sulphate by 75 to 95% from baseline in all patients treated. With doses of 0.5 mg and higher, many values of estrone and estrone sulphate are 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 highly specific in inhibiting aromatase activity. Impairment of adrenal steroidogenesis has not been observed. No clinically relevant changes were found in the plasma concentrations of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxy-progesterone, and ACTH, or in plasma renin activity among postmenopausal patients treated with a daily dose of 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 androgen (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, the same applies to thyroid function assessed by TSH, T4 and T3 uptake testing.

Clinical studies

Adjuvant treatment

Study BIG 1-98

BIG 1-98 was a multi-centre, double-blind study in which over 8000 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 events: defined as loco-regional recurrence, distant metastasis, invasive contraleteral breast cancer, second invasive (non-breast) primary malignancy , or death from any cause without a prior cancer event); 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 months and 60 months
Data in Table 3 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 3 Primary Core Analysis: Disease-free and overall survival, at a median follow-up of 26 months and at median follow-up of 60 months (ITT population)

	Primary Core Analysis					
	Median follow-up 26 months			**Median follow-up 60 months**		
	Letrozole N=4003	**Tamoxifen N=4007**	**HR[1] (95% CI) *P***	**Letrozole N=4003**	**Tamoxifen N=4007**	**HR[1] (95% CI) *P***
Disease-free survival (primary) - events (protocol definition[2])	351	428	0.81 (0.70, 0.93) 0.003	585	664	0.86 (0.77, 0.96) 0.008
Overall survival (secondary) Number of deaths	166	192	0.86 (0.70, 1.06)	330	374	0.87 (0.75, 1.01)

HR = Hazard ratio; CI = Confidence interval
[1] Log rank test, stratified by randomization option and use of chemotherapy (yes/no)
[2] DFS events: loco-regional recurrence, distant metastasis, invasive contralateral breast cancer, second (non-breast) primary malignancy, death from any cause without a prior cancer event.

Results at a median follow-up of 96 months (monotherapy arms only)
The Monotherapy Arms Analysis (MAA) long-term update of the efficacy of letrozole monotherapy compared to tamoxifen monotherapy (median duration of adjuvant treatment: 5 years) is presented in Table 4.

Table 4 Monotherapy Arms Analysis: Disease-free and overall survival at a median follow-up of 96 months (ITT population)

	Letrozole N=2463	**Tamoxifen N=2459**	**Hazard Ratio[1] (95% CI)**	***P* Value**
Disease-free survival events (primary) [2]	626	698	0.87 (0.78, 0.97)	0.01
Time to distant metastasis (secondary)	301	342	0.86 (0.74, 1.01)	0.06
Overall survival (secondary) - deaths	393	436	0.89 (0.77, 1.02)	0.08
Censored analysis of DFS3	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 randomization 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 5).

Table 5 **Sequential treatments analysis of disease-free survival with letrozole as initial endocrine agent (STA switch population)**

	N	Number of events[1]	Hazard ratio[2]	(97.5% confidence interval)	Cox model *P*-value
[Letrozole→]Tamoxifen	**1460**	**254**	**1.03**	**(0.84, 1.26)**	**0.72**
Letrozole	**1464**	**249**			
1 Protocol definition, including second non-breast primary malignancies, after switch / beyond two years 2 Adjusted by chemotherapy use					

There were no significant differences in DFS, OS, SDFS or DDFS in any of the STA from randomization pairwise comparisons (Table 6).

Table 6 **Sequential Treatments Analyses from randomization (STA-R) of disease-free survival (ITT STA-R population)**

	Letrozole→Tamoxifen	Letrozole
Number of patients	1540	1546
Number of patients with DFS events (protocol definition)	330	319
Hazard ratio[1] (99% CI)	1.04 (0.85, 1.27)	
	Letrozole→Tamoxifen	**Tamoxifen[2]**
Number of patients	1540	1548
Number of patients with DFS events (protocol definition)	330	353
Hazard ratio[1] (99% CI)	0.92 (0.75, 1.12)	
[1] Adjusted by chemotherapy use (yes/no) [2] 626 (40%) patients selectively crossed to letrozole after tamoxifen arm unblinded in 2005		

Study D2407
Study D2407 is an open-label, randomized, multicentre post approval safety study designed to compare the effects of adjuvant treatment with letrozole and tamoxifen on bone mineral density (BMD) and serum lipid profiles. A total of 262 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 5 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).

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, 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 nodal status. There was no significant difference in overall survival: (letrozole 51 deaths; placebo 62; HR 0.82; 95% CI 0.56, 1.19).

Consequently, after the first interim analysis the study was unblinded and continued in an open-label fashion and patients in the placebo arm were allowed to switch to letrozole for up to 5 years. Over 60% of eligible patients (disease-free at unblinding) opted to switch to letrozole. The final analysis included 1,551 women who switched from placebo to letrozole at a median of 31 months (range 12 to 106 months) after completion of tamoxifen adjuvant therapy. Median duration for letrozole after switch was 40 months.

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

Table 7 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)[2] *P* value	Letrozole N=2582	Placebo N=2586	HR (95% CI)[2] *P* value
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)
4-year DFS rate	94.4%	89.8%		94.4%	91.4%	
Disease-free survival[3], 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	- -	- -	- -	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 blinded in 2003, 1551 patients in the randomized placebo arm (50%—i.e., disease-free) switched to letrozole at a median of 31 months after randomization. The analyses presented here ignore selective switching.
[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 second year 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 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 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 2.5 mg (letrozole, N=453) to tamoxifen 20 mg (N=454) 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.

Table 8 Results at a median follow-up of 32 months

Variable	Statistic	Letrozole N=453	Tamoxifen N=454
Time to progression	Median	9.4 months	6.0 months
	(95% CI for median)	(8.9, 11.6 months)	(5.4, 6.3 months)
	Hazard ratio (HR)	0.72	
	(95% CI for HR)	(0.62, 0.83)	
		P<0.0001	
Objective response rate (ORR)	Complete answer + Partial answer	145 (32%)	95 (21%)
	(95% CI for rate)	(28, 36%)	(17, 25%)
	Odds ratio	1.78	
	(95% CI for odds ratio)	(1.32, 2.40)	
		P=0.0002	

Time to progression was significantly longer, and response rate significantly higher for letrozole irrespective of whether adjuvant anti-estrogen 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 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-estrogens.

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 found out 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

General properties
LETRASAN (letrozole) is a non-steroidal aromatase inhibitor and antineoplastic agent. Letrozole is white-yellowish crystal powder. Letrozole is freely soluble in dichloromethane and slightly soluble in ethanol. Letrozole is practically insoluble in water.

Absorption:
Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability: 99.9%). Food slightly decreases the rate of absorption (median t_{max} 1 hour fasted versus 2 hours fed; and mean C_{max} 129 ± 20.3 nmol/L fasted versus 98.7 ± 18.6 nmol/l fed). But the extent of absorption [AUC (Area under the curve)] 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 (CYP) isoenzymes CYP3A4 and CYP2A6 were found to be capable of converting letrozole to this metabolite. Formation of minor unidentified metabolites and direct renal and faecal excretion play only a minor role in the overall elimination of letrozole. Within 2 weeks after administration of 2.5 mg ^{14}C-labelled letrozole to healthy postmenopausal volunteers, 88.2 ± 7.6% of the radioactivity was recovered in urine and 3.8 ± 0.9% in faeces. At least 75% of the radioactivity recovered in urine up to 216 hours (84.7 ± 7.8% of the dose) was attributed to the glucuronide of the carbinol metabolite, about 9% to two unidentified metabolites, and 6% to unchanged letrozole.

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

Linearity/non-linearity

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

Characteristics in patients

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_{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 CLcr or an impairment of renal function.

Therefore, no dose adjustment is required for patients with renal impairment (CLcr ≥10 mL/min). Little information is available in patients with severe impairment of renal function (CLcr <10 mL/min).

Hepatic impairment

In a 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 subjects with liver cirrhosis and severe hepatic impairment (Child-Pugh C) to those in eight healthy volunteers AUC and $t_{½}$ increased by 95 and 187%, respectively. Thus, breast cancer patients with severe hepatic impairment are expected to be exposed to higher letrozole levels than patients without severe hepatic dysfunction.

Therefore, letrozole should be administered with caution to patients with severe hepatic impairment and only after evaluating the risk/benefit profile for each patient.

Pediatric population:

LETRASAN is not used in children.

Geriatric population:

Age has not been observed to affect the pharmacokinetics of letrozole.

5.3. Preclinical safety data

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

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

In repeated-dose toxicity studies in rats and dogs up to 12 months, the main findings observed can

be attributed to the pharmacological action of the compound. The no-adverse-effect level was 0.3 mg/kg in both species.

Oral administration of letrozole to female rats resulted in decreases in mating and pregnancy ratios and increases in pre-implantation loss.
Both *in vitro* and *in vivo* investigations 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 has shown embryotoxic and fetotoxic effects in pregnant rats and rabbits after 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 cervical/centrum vertebral fusion. An increased incidence of fetal malformations was not seen in the rabbit. 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 are limited to pharmacological effects known from animal studies and relevant only to safe human use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Maize starch
Lactose monohydrate (from cow milk)
Sodium starch glycolate
Microcrystalline cellulose PH 102
Magnesium stearate

Film-coating material: Opadry II Yellow
Polyvinyl alcohol
Polyethylene glycol
Titanium dioxide
Talc
Yellow iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage
Store at room temperature below 25°C.

6.5 Nature and contents of container
PVC/PE/PVDC blisters.
Blister package containing 30 film-coated tablets

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

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