Letrozole

Non-steroidal aromatase inhibitor (inhibitor of estrogen biosynthesis) antineoplastic agent

DESCRIPTION AND COMPOSITION

Pharmaceutical form
Film-coated tablets.
Coated tablet: dark yellow, round, slightly biconvex with beveled edges. One side bears a score line. Diameter: approx. 10 mm.

Active substance
4,4'-[(1H-1,2,4-triazol-1-yl)-methylene]bis-benzonitrile (INN/USAN: letrozole).
Each film-coated tablet contains 2.5 mg letrozole.

Excipients
Colloidal anhydrous silica, microcrystalline cellulose, lactose monohydrate, magnesium stearate, maize starch, macrogol 6000, talcum, titanium dioxide (E 171), hypromellose, polyethylene glycol 8000, iron oxides, cinnamon oil (E 172), non-coloring glue (E 1519).
Pharmaceutical formulations may vary between countries.

INDICATIONS

Letrozole is not indicated in hormone receptor-negative disease.

Adjuvant treatment
- Adjuvant treatment of postmenopausal women with hormone receptor-positive invasive early breast cancer.
- Adjuvant extended treatment of invasive early breast cancer in post-menopausal women who have completed standard adjuvant tamoxifen therapy for five years.

- First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer.
- Advanced breast cancer after relapse or disease progression, in women with natural or artificially induced postmenopausal endocrine status, who have previously been treated with antiestrogens.
- Non-adjuvant treatment of advanced breast cancer with hormone receptor-positive, HER-2 negative breast cancer where chemotherapy is not suitable and immediate surgery not indicated.

DOSAGE PATTERN AND ADMINISTRATION

Dosage regimen

General target population
Adults
The recommended dose of letrozole is 2.5 mg once daily. In the adjuvant and extended adjuvant setting, treatment with letrozole should continue for 5 years or until disease recurrence/progression. In the adjuvant setting, the duration of treatment with letrozole versus tamoxifen in the adjuvant setting, no benefit in efficacy or safety was obtained by treatment for more than 5 years. In the extended adjuvant setting, letrozole is given continuously for 5 years. In patients with metastatic disease, treatment with letrozole should continue until tumor progression is evident. In the adjuvant and extended adjuvant setting, treatment with letrozole should be continued for 2 to 5 months in order to establish optimal tumor reduction. If the response is not adequate, treatment with letrozole should be discontinued, surgery scheduled and/or further treatment options discussed with the patient.

Special populations
Elderly patients
No dose adjustment of letrozole is required for patients with mild to moderate hepatic/renal/kidney (CrCl 30-60 ml/min). Insufficient data are available for patients with severe renal/kidney impairment (CrCl < 30 ml/min). Letrozole should be used with caution in CL/renal/liver/ kidney impairment (see sections WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY – Pharmacokinetics).

Renal impairment
No dosage adjustment of letrozole is required for patients with renal insufficiency with creatinine clearance (CrCl) ≥10 ml/min. Insufficient data are available in cases of renal insufficiency with CrCl < 10 ml/min. Letrozole should be used with caution (see sections CLINICAL PHARMACOLOGY – Pharmacokinetics).

Pediatric patients
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 no recommendation on a posology can be made.

Elderly patients (aged 65 and older)
No dose adjustment is required for elderly patients.

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.

Duration of use
The related 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 take the next dose at the usual time. Do not take a double dose to make up for a missed dose. Doses over the 2.5 mg recommended dose, even proportionally, to systemic exposure rate observed (see section CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

- Known hypersensitivity to the active substance or to any of the excipients.
- Premenopausal women (see sections WARNINGS AND PRECAUTIONS, PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

WARNINGS AND PRECAUTIONS

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

Hepatic impairment
In patients with severe hepatic impairment (Child-Pugh score C), systemic exposure and elimination half-life are increased compared to those observed in healthy volunteers. Such patients should therefore be kept under close supervision (see section CLINICAL PHARMACOLOGY – Pharmacokinetics).

Bone effects
Osteoporosis and/or bone fractures have been reported with the use of letrozole. Therefore consideration of related bone health is recommended during treatment (see sections ADVERSE EFFECTS and CLINICAL PHARMACOLOGY – Pharmacodynamics).

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

Fertility
Due to pharmacological action of letrozole is to reduce estrogen production by aromatase inhibition. In postmenopausal women, the inhibition of estrogen synthesis leads to feedback increase in gonadotropin (LH, FSH) levels. Increased FSH levels in turn stimulate follicular development and reduce ovulation.

Interactions
Co-administration of letrozole with tamoxifen, other anti-estrogens or estrogen-containing products should be avoided since these may reduce the efficacy of letrozole by competition of letrozole. The mechanism of this interaction is unknown (see section INTERACTIONS).

Driving and using machines
No adverse effect on driving has been observed with the use of letrozole and convalescence has been reported occasionally, caution is advised when driving or using machine.

ADVERSE DRUG REACTIONS

Summary of the safety profile
Letrozole was generally well tolerated across all studies as first-line and second-line treatment of advanced breast cancer in postmenopausal women, as adjuvant and as extended adjuvant treatment in women who have received prior standard adjuvant therapy with tamoxifen. Approximately one third of the patients treated with letrozole in the extended adjuvant setting experienced adverse events, which were mild in intensity. In the setting for both letrozole and tamoxifen arms, as a median treatment duration of 2 years, the most frequently reported adverse reactions in the letrozole and tamoxifen treated and placebo arms, at a median treatment duration of 60 months) experienced hot flashes (letrozole 17.7% versus 14.3% for placebo). Adverse events were for the most in nature, and may an association with estrogen deprivation.

The most frequently reported adverse reactions in the clinical studies were hot flashes, arthralgia/arthritis, fatigue (including asthenia), headache, and nausea. These are pharmacological consequences of estrogen deprivation (e.g. hot flashes, alopecia and vaginal bleeding). The following adverse drug reactions, listed in Table 1, were reported during treatment with letrozole in controlled clinical studies and post-marketing.

Table 1 Tabulated summary of adverse drug reactions from clinical trials and from post-marketing experience with letrozole

Adverse drug reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥10), uncommon (≥1 to <10), uncommon (≥1/100 to <1%), rare (≥0.01 to <0.1%), very rare (<0.01%), not known (cannot be estimated from the available data).

Table 1 - Adverse drug reactions	
Infections and infestations	
Uncommon	Urinary tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon	Benign cyst
Blood and the lymphatic system disorders	
Uncommon	Leukopenia
Immune system disorders	
Not known	Anaphylactic reaction
Metabolism and nutrition disorders	
Very common	Hypercholesterolemia
Common	Decreased appetite, increased appetite
Psychiatric disorders	
Common	Depression
Uncommon	Anxiety (including nervousness), irritability
Nervous system disorders	
Common	Headache, dizziness, vertigo
Uncommon	Paresthesia, insomnia, memory impairment, dysaesthesia (including paresthesia, hypaesthesia), dysgeusia, cerebrovascular accident, carpal tunnel syndrome
Eye disorders	
Uncommon	Cataract, eye irritation, blurred vision
Cardiac disorders	
Common	Palpitations
Uncommon	Angina pectoris, ischemic cardiac events (including new or worsening angina, angina requiring surgery, myocardial infarction and myocardial ischemia)
Vascular disorders	
Very common	Hot flush
Common	Hypertension
Uncommon	Thromboembolic (including superficial and deep vein thrombosis), vasospasm, hypertensive crisis, arterial thrombosis, cerebral infarction
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, cough
Gastrointestinal disorders	
Common	Nausea, vomiting, dyspepsia, constipation, diarrhoea, abdominal pain
Uncommon	Stomatitis, dry mouth
Hepatobiliary disorders	
Uncommon	Increased hepatic enzymes, hyperbilirubinaemia, jaundice
Very rare	Hepatitis
Skin and subcutaneous tissue disorders	
Very common	Hyperhidrosis
Common	Alopecia, dry skin, rash (including erythematous, maculopapular, pustulform, and vesicular rash)
Uncommon	Pruritus, urticaria
Very rare	Erythema multiforme, cutaneous vasculitis, erythema nodosum
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia
Common	Myalgia, bone pain, osteoporosis, bone fractures, arthritis, back pain
Reproductive system and breast disorders	
Not known	Tingler finger
Renal and urinary disorders	
Uncommon	Pollakiuria
Reproductive system and breast disorders	
Common	Vaginal haemorrhage
Uncommon	Vaginal discharge, vulvovaginal dryness, breast pain
General disorders and administration site conditions	
Very common	Fatigue (including asthenia, malaise)
Common	Peripheral oedema, chest pain
Uncommon	General oedema, pyrexia, mucosal dryness, thirst
Investigations	
Common	Weight increased
Uncommon	Weight decreased
Injury, poisoning and procedural complications	
Common*	Fall

* Adverse drug reactions reported only in the extended setting
Adverse drug reactions in the adjuvant setting
* In some cases fall was reported as a consequence of other adverse events such as dizziness and vertigo.

Description of selected adverse drug reactions
Cardiac adverse reactions
In the letrozole arm, in addition to the data presented in Table 2, the following adverse events were reported for letrozole and tamoxifen, respectively (reaction treatment duration in 5 years): angina requiring surgery (0.6% vs. 1.0%), cardiac failure (0.7% vs. 0.9%), ischemic cardiac events (1.7% vs.1.7%), cerebrovascular accident/transient ischemia attack (2.1% vs. 1.8%).

In the extended adjuvant setting for letrozole (median duration of treatment 5 years) and placebo (median duration of treatment 60 months), the following adverse events were (0.6% vs. 0.8%) rate of congestive heart (1.4% vs. 1.0%) myocardial infarction (1.0% vs. 0.8%), angina pectoris (0.7% vs. 0.8%), cerebrovascular disorders (2.1% vs. 2.0% vs. 3.0%) were reported.

Letrozole treated patients statistically significantly different in the two treatment arms.

Skeletal adverse reactions
For skeletal safety data from the adjuvant setting, please refer to Table 6.

In the extended adjuvant setting, significantly more patients treated with letrozole experienced bone fractures or osteoporosis (bone fractures, 10.0% and osteoporosis, 9.4%) versus placebo treated patients (bone fractures, 6.4% and osteoporosis, 3.2%) (median duration of treatment was 5 years for letrozole, compared with 5 years for placebo).

INTERACTIONS

Letrozole is only metabolized in the liver and the cytochrome P450 enzymes CYP3A4 and CYP2A6 mediate the metabolic clearance of letrozole. Therefore, this suggests alternation of letrozole clearance by other active substances that affect CYP3A4 and CYP2A6 activity. The metabolism of letrozole appears to have a low affinity for CYP3A4 because the enzyme could be saturated only at relatively high concentrations. CYP2A6 seems to be responsible for letrozole at steady-state in the typical clinical situation.

Effects of other active substances on the pharmacokinetics
Inhibitors of CYP450 and CYP3A4 activities could decrease the metabolism of letrozole and thereby increase plasma concentrations of letrozole. The concomitant administration of potent cytochrome P450 inhibitors (for example, with strong inhibitory activity such as but limited to ketoconazole, bifonazole, voriconazole, ritonavir, clarithromycin, and lathmoxyfen, CYP2A6 (e.g. methoxsalen), may increase exposure to letrozole. Therefore caution is recommended if patients for whom strong CYP2A6 and CYP3A4 inhibitors are administered.

Drugs that may decrease blood serum concentrations
Co-administration of letrozole with strong inhibitors of aromatase of letrozole and thereby decrease CYP3A4 activities of letrozole. The concomitant administration of medicines that reduce CYP3A4 (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital, and herbal products containing hypericum perforatum (St. John's wort)) in breast cancer patients for whom strong CYP3A4 inhibitors are administered the drug reduces is known to induce CYP3A4.

Co-administration of letrozole (2.5mg) and tamoxifen 20 mg daily resulted in a reduction of letrozole plasma levels by 38% on average. Clinical experience in the second line breast cancer treatment with 2.5 mg letrozole and 20 mg tamoxifen daily, the concomitant consumption of letrozole reactions is increased if letrozole is administered immediately after tamoxifen treatment. Letrozole is not recommended.

Drugs that may have their systemic serum concentrations altered by letrozole
In vitro, letrozole inhibits the cytochrome P450 isoenzymes CYP2A6 and, moderately, CYP2C19 and CYP2C19 activities. Letrozole should be used with caution when it is given in combination with medicinal products, whose elimination is mainly dependent on CYP2C19 and whose therapeutic index is narrow (e.g. phenytoin, mephenytoin, S-mephenytoin, lansoprazole, omeprazole, and diazepam).

Clinical interaction studies with substrates for CYP2C9 with a narrow therapeutic index (warfarin) and warfarin (sensitive substrate for CYP2C9 with a narrow therapeutic window) have not been performed. Letrozole should be used with caution when it is given in combination with the coadministration of letrozole with these drugs does not result in clinically significant drug interactions.

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

Pregnancy, lactation, females and males of reproductive potential

Pregnancy
Letrozole is contraindicated during pregnancy (see section CONTRAINDICATIONS). There are post-marketing reports of spontaneous abortions and congenital anomalies in infants born to patients treated with letrozole (see sections WARNINGS AND PRECAUTIONS) during pregnancy.

Isolated cases of birth defects (facial tumor, ventricular septal defect) have been reported in infants born to pregnant women exposed to off-label use (infertility treatment), isolated induction of letrozole.

Lactation
Letrozole is contraindicated during lactation (see section CONTRAINDICATIONS).

Females and males of reproductive potential
The physician needs to discuss the necessity of adequate contraception with women who are of reproductive potential. Letrozole should not be used in premenopausal or perimenopausal or recently became postmenopausal, until their postmenopausal status is fully established.

OVERDOSAGE

Isolated cases of overdosage with letrozole have been reported.

The first planned interim analysis at a median follow-up of around 28 months (25% of events) the treatment arm of letrozole 2.5 mg versus the placebo arm, disease-free survival (DFS) was statistically significantly superior (HR = 0.76; 95% CI: 0.62 – 0.93; P=0.0066). The benefit in favor of letrozole was observed regardless of hormone receptor status. The difference in overall survival (between 57 deaths: letrozole 29 versus 28 placebo) was not significant.

Consequently, after first interim analysis the study was unblinded and continued in an open-label fashion. Patients who were randomized to receive placebo for 2 years switched to letrozole for 3 years. Patients who opted not to switch were followed by observation only. Over 80% of the patients in the letrozole arm continued treatment for the 5 years. The final analysis included 1,203 women who switched from placebo to letrozole at a median of 2 years (range: 0.1 – 3.1 years) and who received letrozole as tamoxifen adjuvant therapy. Median duration of letrozole after switch was 28 months.

The final analysis conducted at a median follow-up of 62 months confirmed the significant benefit of letrozole versus placebo in disease-free survival.

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

	Median follow-up 28 months			Median follow-up 62 months		
	Letrozole N=1,286	Placebo N=1,290	HR (95% CI)* P-value	Letrozole N=1,262	Placebo N=1,268	HR (95% CI)* P-value
Disease-free survival						
Events	62 (2.64%)	100 (8.0%)	0.58 (0.43, 0.78) P=0.0066	209 (8.1%)	298 (11.1%)	0.76 (0.62, 0.94)
3-year DFS rate	94.0%	88.8%		76.0%	61.9%	
Distant disease-free survival including deaths from any cause						
Events	120 (5.7%)	160 (7.9%)	0.62 (0.49, 0.78)	342 (13.5%)	420 (16.9%)	0.68 (0.77, 1.05)
5-year DFS rate	93.5%	85.8%		66.8%	56.7%	
Overall survival						
Events	57 (2.2%)	50 (2.6%)	0.61 (0.44, 0.85)	112 (5.7%)	128 (6.4%)	0.86 (0.70, 1.05)
Overall survival						
Deaths	51 (2.0%)	62 (2.4%)	0.82 (0.56, 1.19)	208 (8.1%)	232 (9.0%)	0.19 (0.80, 1.06)
Deaths*	– – – –	– – – –		208* (8.1%)	179* (6.95%)	0.78 (0.64, 0.94)*

HR – Hazard ratio; CI – Confidence interval
* Often the study was unblinded in 2005, 1,357 patients in the randomized placebo and letrozole arms had switched to open-label letrozole treatment, and data were censored at 2 months after randomization. The analysis presented here ignore that selection bias.
* Stratified by receptor status, nodal status and prior adjuvant chemotherapy.
* Stratified by receptor status, nodal status and prior adjuvant chemotherapy.
* Distant disease-free survival events: bone regional recurrence, distant metastasis or contralateral breast cancer.
* Exploratory analysis, censoring follow-up times at the date of switch (51 occurred in the letrozole arm).
* Median follow-up 62 months.
* Deaths: letrozole 208 versus 232 (occurred 2.7 months

In the MA-17 trial subsidy in which concomitant adriam 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 5 years and was in total hip (-2.4% versus -0.6%, P=0.0009). Fracture rates were similar between arms.

In the MA-17 trial subsidy there were no significant differences between letrozole and placebo in total cholesterol or in any lipid fraction.

In the MA-17 trial subsidy there were no significant differences between treatments in physical component summary score or mental component summary score, or in any domain scores in the SF-36 scale. In the BIG98-2B, letrozole significantly improved vasomotor symptoms, vaginal dryness, and musculoskeletal symptoms, and the rate of treatment by these symptoms deriving from estrogen deprivation – hot flashes and vaginal dryness – was lower in letrozole treated patients. In the MA-17 trial series, no ending reviews, with a statistically significant difference in favor of placebo.

Study CFEMANE PSD
A double blind trial (PSD) was conducted in 907 postmenopausal breast cancer patients randomly allocated either letrozole 2.5 mg for 4 months or tamoxifen for 4 months. At the time of randomization, the median age was 70 years (range: 50 – 92 years). Half of the patients would have qualified for breast-conserving surgery. Based on clinical assessment, 67% of the patients had cT2 tumors, 18% had cT3 and 15% had cT1 tumors (tamoxifen and P=0.02). The finding was consistently confirmed by ultrasound (letrozole 26% vs tamoxifen 35%, P=0.02) and mammography (letrozole 30% vs tamoxifen 16%, P=0.0001). Letrozole was more effective than tamoxifen in reducing the tumor size (letrozole group P=0.02) underwent breast conserving therapy). During the 4 month pre-operative treatment period, 2 patients in the letrozole group and 1 patient (0.1%) of patients treated with tamoxifen had disease progression on clinical assessment.

First line treatment

Study CFEMANE PSD
A 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 response rate (secondary endpoint) in the intent-to-treat (ITT) population. The results are summarized in Table 3.

Table 3 Results at a median follow-up of 32 months

Variable	Letrozole	Tamoxifen	Letrozole	Tamoxifen
Time to progression	**Median**		**95 % CI**	
	(95% CI for median)		(9.6, 11.6 months)	(5.4, 6.5 months)
	Hazard ratio (HR)		0.72	
	(95 % CI for HR)		(0.62, 0.83)	
			P=0.0001	
Objective response rate (ORR)	**CR+PR**	**140 (30%)**	**99 (21%)**	
	(95% CI for rate)	(26, 34%)	(17, 25%)	
	Odds ratio	1.6		
	(95% CI for odds ratio)		(1.20, 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). Letrozole treated patients had a 28% reduced risk of disease progression or death of disease. Median time to progression was 10.1 months for letrozole and 6.5 months for tamoxifen in patients with soft tissue disease only and median 8.3 months for letrozole and 5.5 months for tamoxifen treated patients with visceral disease.

Study design allowed patients to cross over upon progression to the other therapy or alternatives from the study. Approximately 50% of patients crossed over to the other treatment, 2 times more letrozole patients than tamoxifen. 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 survival time of 38 months versus 34 months for tamoxifen treated patients (P=0.0421). 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.

Study ARIMIDEX
No statistical significant differences were observed in favor of letrozole 2.5 mg compared to megestrol acetate: overall objective tumor response rate (ORR) is 19% (P=0.06), and in time to treatment failure (P=0.02). Overall survival and time to progression was not significantly different between the 2 arms (P=0.2 and P=0.07, respectively).

Study ARIMIDEX
Letrozole 2.5 mg was statistically superior to aminoglutethimide 250 mg tid for time to treatment failure (P=0.0003), time to progression (P=0.0003) and overall survival (P=0.0003). In this study, the response rate was not significantly different between letrozole 2.5 mg and aminoglutethimide (P=0.06).

Carcinoma in situ
Data available to date with non-breast cancer but not been studied.

NON-CLINICAL SAFETY DATA

In a variety of preclinical safety studies conducted in standard animal species, there was no evidence of toxicity specific to letrozole.

Letrozole showed a low degree of acute toxicity in rodents exposed to up to 2000 mg/kg, and no mortality occurred at a dose of 2000 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-effect dose was 0.1 mg/kg in the most sensitive species.

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

The pharmacological effects of letrozole resulted in skeletal, reproductive and endocrine changes in the female rat. The no-effect dose for these effects was 0.1 mg/kg and from the lowest dose (0.001 mg/kg/day) in male and increased from the lowest dose (0.1 mg/kg/day) in female rats. Letrozole was well tolerated by the reproductive tract in females. In the same study, decreased fertility of all doses was accompanied by decreased ovulation, increased pre-implantation loss, decreased corpora lutea, luteinizing hormone, follicle stimulation and atrophy of the female reproductive tract. With the exception of bone sex in females and morphological changes in the testes, all effects were at least partially reversible.

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	(95% CI for odds ratio)		(1.20, 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). Letrozole treated patients had a 28% reduced risk of disease progression or death of disease. Median time to progression was 10.1 months for letrozole and 6.5 months for tamoxifen in patients with soft tissue disease only and median 8.3 months for letrozole and 5.5 months for tamoxifen treated patients with visceral disease.

Study design allowed patients to cross over upon progression to the other therapy or alternatives from the study. Approximately 50% of patients crossed over to the other treatment, 2 times more letrozole patients than tamoxifen. 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 survival time of 38 months versus 34 months for tamoxifen treated patients (P=0.0421). 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.

Study ARIMIDEX
No statistical significant differences were observed in favor of letrozole 2.5 mg compared to megestrol acetate: overall objective tumor response rate (ORR) is 19% (P=0.06), and in time to treatment failure (P=0.02). Overall survival and time to progression was not significantly different between the 2 arms (P=0.2 and P=0.07, respectively).

Study ARIMIDEX
Letrozole 2.5 mg was statistically superior to aminoglutethimide 250 mg tid for time to treatment failure (P=0.0003), time to progression (P=0.0003) and overall survival (P=0.0003). In this study, the response rate was not significantly different between letrozole 2.5 mg and aminoglutethimide (P=0.06).

Carcinoma in situ
Data available to date with non-breast cancer but not been studied.

NON-CLINICAL SAFETY DATA

In a variety of preclinical safety studies conducted in standard animal species, there was no evidence of toxicity specific to letrozole.

Letrozole showed a low degree of acute toxicity in rodents exposed to up to 2000 mg/kg, and no mortality occurred at a dose of 2000 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-effect dose was 0.1 mg/kg in the most sensitive species.

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

The pharmacological effects of letrozole resulted in skeletal, reproductive and endocrine changes in the female rat. The no-effect dose for these effects was 0.1 mg/kg and from the lowest dose (0.001 mg/kg/day) in male and increased from the lowest dose (0.1 mg/kg/day) in female rats. Letrozole was well tolerated by the reproductive tract in females. In the same study, decreased fertility of all doses was accompanied by decreased ovulation, increased pre-implantation loss, decreased corpora lutea, luteinizing hormone, follicle stimulation and atrophy of the female reproductive tract. With the exception of bone sex in females and morphological changes in the testes, all effects were at least partially reversible.

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

In a 104 week rat carcinogenicity study, no treatment-related tumors were noted in male rats. In female rats, letrozole induced a dose-dependent increase in the incidence of benign and malignant uterine tumors.

In a 104 week carcinogenicity study, no treatment-related tumors were noted in male mice. In female mice, a generally dose-related increase in the incidence of benign and malignant ovarian tumors was observed. The ovarian and uterine tumors in female rats 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.

Oral administration of letrozole to pyrol Sprague-Dawley rats resulted in a slight increase in the incidence of fetal malformation (domed head and beed ventricumbilical anomaly) and decreased fetal weight at a dose causing severe maternal toxicity (0.1 mg/kg/day). However, it was not possible to show whether this was an indirect consequence of the pharmacological action of letrozole on the maternal animal or a direct effect of letrozole on the embryo. In rats, rabbits (see sections CONTRAINDICATIONS and PREGNANCY), letrozole crosses the placenta and is found in the fetal circulation.

Preclinical observations were confirmed to be linked associated with the recognized pharmacological action, which is the only safety concern for human use derived from animal studies.

INCOMPATIBILITIES

Not applicable.

STORAGE

See listing box.
Letrozole should not be used after the date marked "EXP" on the pack.
Letrozole must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

No specific instructions for use/handling.

Manufacturer:
See listing box.

International Package Leaflet
Information issued: December 2010
Novartis Pharma AG
Novartis Pharma AG, Basel, Switzerland

NOVARTIS
Faller
August Faller Artwork Studios GmbH
Postfach 30 40
D-79113 Freiburg i.Br.
www.aug-faller.com
Job Name: Letrozole
Comp. Description: Leaflet FILM/AIA (LIF PACKS)
Comp. No. Size: 210 x 297 mm
Comp. No. Type: 2 Side Print
Comp. No. Qty: 2 Different
Tech. Drawing No.: 6024-9135_06
Tech. Drawing Date: 2.12.2010
Tech. Drawing Name: Jan Schmidt
Date
Drawing No.: 6024-9135
Customer: Sandoz
Contact: Jan Schmidt
Printing Colours: Black
Technical Colours: Coating UV-Lack
Varnish
Material: Leaflet Paper 40 g
Font Size: 4, 20, 22
Font Type: Helvetica Neue Light, Helvetica Neue Light Italic, Helvetica Neue Bold, Helvetica Neue Bold Italic
Special Instructions: Perforation
!PLEASE TURN OVERPRINTING ON!