1.5 Product Information

1.5.1 Prescribing Information

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

LETERO (Letrozole Tablets USP 2.5 mg)

Strength: 2.5 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains: 2.5 mg of Letrozole USP

3. PHARMACEUTICAL FORM

Dosage form: Film coated tablet

Description: Dark yellow coloured, round shaped, slightly biconvex bevel edged film coated tablets debossed with '5' on one side and 'H' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adjuvant Treatment of Early Breast Cancer

Letrozole Tablets 2.5 mg (letrozole) is indicated for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.

Extended Adjuvant Treatment of Early Breast Cancer

Letrozole Tablets 2.5 mg is indicated for the extended adjuvant treatment of early breast cancer in postmenopausal women, who have received 5 years of adjuvant tamoxifen therapy. The effectiveness of Letrozole Tablets 2.5 mg in extended adjuvant treatment of early breast cancer is based on an analysis of disease-free survival in patients treated with Letrozole Tablets 2.5 mg for a median of 60 months

First and Second-Line Treatment of Advanced Breast Cancer

Letrozole Tablets 2.5 mg is indicated for first-line treatment of postmenopausal women with hormone receptor positive or unknown, locally advanced or metastatic breast cancer.

Letrozole Tablets 2.5 mg is also indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy

4.2 Posology and method of administration

Recommended Dose

The recommended dose of Letrozole Tablets 2.5 mg is one 2.5 mg tablet administered once a day, without regard to meals.

Use in Adjuvant Treatment of Early Breast Cancer

In the adjuvant setting, the optimal duration of treatment with letrozole is unknown. In both the adjuvant study and the post approval adjuvant study, median treatment duration was 5 years. Treatment should be discontinued at relapse

Use in Extended Adjuvant Treatment of Early Breast Cancer

In the extended adjuvant setting, the optimal treatment duration with Letrozole Tablets 2.5 mg is not known. The planned duration of treatment in the study was 5 years. In the final updated analysis, conducted at a median follow-up of 62 months, the median treatment duration for Letrozole Tablets 2.5 mg was 60 months. Seventy-one (71%) percent of patients were treated for at least 3 years and 58% of patients completed at least 4.5 years of extended adjuvant treatment. The treatment should be discontinued at tumor relapse

Use in First and Second-Line Treatment of Advanced Breast Cancer

In patients with advanced disease, treatment with Letrozole Tablets 2.5 mg should continue until tumor progression is evident

Use in Hepatic Impairment

No dosage adjustment is recommended for patients with mild to moderate hepatic impairment, although Letrozole Tablets 2.5 mg blood concentrations were modestly increased in subjects with moderate hepatic impairment due to cirrhosis. The dose of Letrozole Tablets 2.5 mg in patients with cirrhosis and severe hepatic dysfunction should be reduced by 50%. The recommended dose of Letrozole Tablets 2.5 mg for such patients is 2.5 mg administered every other day. The effect of hepatic impairment on Letrozole Tablets 2.5

mg exposure in noncirrhotic cancer patients with elevated bilirubin levels has not been determined.

Use in Renal Impairment

No dosage adjustment is required for patients with renal impairment if creatinine clearance is greater than or equal to 10 mL/min

4.3 Contraindications

- Pregnancy: Letrozole can cause fetal harm.
- Known hypersensitivity to the active substance, or to any of the excipients.

4.4 Special warnings and precautions for use

Bone Effects

Use of Letrozole Tablets 2.5 mg may cause decreases in bone mineral density (BMD). Consideration should be given to monitoring BMD. Results of a safety study to evaluate safety in the adjuvant setting comparing the effect on lumbar spine (L2-L4) BMD of adjuvant treatment with letrozole to that with tamoxifen showed at 24 months a median decrease in lumbar spine BMD of 4.1% in the letrozole arm compared to a median increase of 0.3% in the tamoxifen arm (difference = 4.4%) ($P < 0.0001$). Updated results from the BMD substudy (MA-17B) in the extended adjuvant setting demonstrated that at 2 years patients receiving letrozole had a median decrease from baseline of 3.8% in hip BMD compared to a median decrease of 2.0% in the placebo group. The changes from baseline in lumbar spine BMD in letrozole and placebo treated groups were not significantly different .

In the adjuvant trial (BIG 1-98) the incidence of bone fractures at any time after randomization was 14.7% for letrozole and 11.4% for tamoxifen at a median follow-up of 96 months. The incidence of osteoporosis was 5.1% for letrozole and 2.7% for tamoxifen. In the extended adjuvant trial (MA-17), the incidence of bone fractures at any time after randomization was 13.3% for letrozole and 7.8% for placebo at a median follow-up of 62 months. The incidence of new osteoporosis was 14.5% for letrozole and 7.8% for placebo.

Cholesterol

Consideration should be given to monitoring serum cholesterol. In the adjuvant trial (BIG 1-98), hypercholesterolemia was reported in 52.3% of letrozole patients and 28.6% of tamoxifen patients. Grade 3-4 hypercholesterolemia was reported in 0.4% of letrozole patients and 0.1% of tamoxifen patients. Also in the adjuvant setting, an increase of greater than or equal to 1.5 x upper limit of normal (ULN) in total cholesterol (generally nonfasting) was observed in patients on monotherapy who had baseline total serum cholesterol within the normal range (i.e., less than =1.5 x ULN) in 155/1843 (8.4%) patients on letrozole vs 71/1840 (3.9%) patients on tamoxifen Lipid lowering medications were required for 29% of patients on letrozole and 20% on tamoxifen .

Hepatic Impairment

Subjects with cirrhosis and severe hepatic impairment who were dosed with 2.5 mg of Letrozole Tablets 2.5 mg experienced approximately twice the exposure to Letrozole Tablets 2.5 mg as healthy volunteers with normal liver function . Therefore, a dose reduction is recommended for this patient population. The effect of hepatic impairment on Letrozole Tablets 2.5 mg exposure in cancer patients with elevated bilirubin levels has not been determined .

Fatigue and Dizziness

Because fatigue, dizziness, and somnolence have been reported with the use of Letrozole Tablets 2.5 mg, caution is advised when driving or using machinery until it is known how the patient reacts to Letrozole Tablets 2.5 mg use.

Laboratory Test Abnormalities

No dose-related effect of Letrozole Tablets 2.5 mg on any hematologic or clinical chemistry parameter was evident. Moderate decreases in lymphocyte counts, of uncertain clinical significance, were observed in some patients receiving Letrozole Tablets 2.5 mg 2.5 mg. This depression was transient in about half of those affected. Two patients on Letrozole Tablets 2.5 mg developed thrombocytopenia; relationship to the study drug was unclear. Patient

withdrawal due to laboratory abnormalities, whether related to study treatment or not was infrequent.

Embryo-Fetal Toxicity

Based on post-marketing reports, findings from animal studies and the mechanism of action, Letrozole Tablets 2.5 mg can cause fetal harm and is contraindicated for use in pregnant women. In post-marketing reports, use of letrozole during pregnancy resulted in cases of spontaneous abortions and congenital birth defects. Letrozole caused embryo-fetal toxicities in rats and rabbits at maternal exposures that were below the maximum recommended human dose (MHRD) on a mg/m^2 basis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during therapy with Letrozole Tablets 2.5 mg and for at least 3 weeks after the last dose.

4.5 Interaction with other medicinal products and other forms of interaction

Tamoxifen

Coadministration of Letrozole Tablets 2.5 mg and tamoxifen 20 mg daily resulted in a reduction of letrozole plasma levels of 38% on average (study P015). Clinical experience in the second-line breast cancer trials (AR/BC2 and AR/BC3) indicates that the therapeutic effect of Letrozole Tablets 2.5 mg therapy is not impaired if Letrozole Tablets 2.5 mg is administered immediately after tamoxifen.

Cimetidine

A pharmacokinetic interaction study with cimetidine (study P004) showed no clinically significant effect on letrozole pharmacokinetics.

Warfarin

An interaction study (P017) with warfarin showed no clinically significant effect of letrozole on warfarin pharmacokinetics.

Other anticancer agents

There is no clinical experience to date on the use of Letrozole Tablets 2.5 mg in combination with other anticancer agents.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy

Risk Summary

Based on postmarketing reports, findings from animal studies and the mechanism of action, Letrozole Tablets 2.5 mg can cause fetal harm and is contraindicated for use in pregnant women. In post-marketing reports, use of letrozole during pregnancy resulted in cases of spontaneous abortions and congenital birth defects; however, the data are insufficient to inform a drug-associated risk.

In animal reproduction studies, administration of letrozole to pregnant animals during organogenesis resulted in increased post-implantation pregnancy loss and resorption, fewer live fetuses, and fetal malformation affecting the renal and skeletal systems in rats and rabbits at doses approximately 0.1 times the daily maximum recommended human dose (MRHD) on a mg/m^2 basis.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Data

Animal Data

In a fertility and early embryonic development toxicity study in female rats, oral administration of letrozole starting 2 weeks before mating until pregnancy day 6 resulted in an increase in pre-implantation loss at doses ≥ 0.003 mg/kg/day (approximately 0.01 times the maximum recommended human dose on a mg/m^2 basis).

In an embryo-fetal developmental toxicity study in rats, daily administration of oral letrozole during the period of organogenesis at doses ≥ 0.003 mg/kg (approximately 0.01 time the maximum recommended human dose on a mg/m^2 basis) resulted in embryo-fetal toxicity including intrauterine mortality, increased resorptions and postimplantation loss, decreased numbers of live fetuses and fetal anomalies including absence and shortening of renal papilla, dilation of ureter, edema and incomplete ossification of frontal skull and metatarsals. Letrozole was teratogenic to rats at a dose of 0.03 mg/kg (approximately 0.01 times the

maximum recommended human dose on a mg/m^2 basis) and caused fetal domed head and cervical/centrum vertebral fusion.

In the embryo-fetal development toxicity study in rabbits, daily administration of oral letrozole during the period of organogenesis at doses ≥ 0.002 mg/kg (approximately 0.01 times the maximum recommended human dose on a mg/m^2 basis) resulted in embryo-fetal toxicity including intrauterine mortality, increased resorption, increased postimplantation loss and decreased numbers of live fetuses. Fetal anomalies included incomplete ossification of the skull, sternebrae, and fore- and hind legs.

Breast-feeding

Risk Summary

It is not known if letrozole is present in human milk. There are no data on the effects of letrozole on the breastfed infant or milk production. Exposure of lactating rats to letrozole was associated with impaired reproductive performance of the male off spring . Because of the potential for serious adverse reactions in breastfed infants from Letrozole Tablets 2.5 mg, advise lactating women not to breastfeed while taking Letrozole Tablets 2.5 mg and for at least 3 weeks after the last dose.

Data

Animal Data

In a postnatal developmental toxicity study in lactating rats, letrozole was administered orally at doses of 1, 0.003, 0.03 or 0.3 mg/kg/day on day 0 through day 20 of lactation. The reproductive performance of the male offspring was impaired at letrozole dose as low as 0.003 mg/kg/day (approximately 0.01 times the maximum recommended human dose on a mg/m^2 basis), as reflected by decreased mating and pregnancy ratios. There were no effects on the reproductive performance of female offspring.

Fertility

Females

Based on studies in female animals, Letrozole Tablets 2.5 mg may impair fertility in females of reproductive potential .

Males

Based on studies in male animals, Letrozole Tablets 2.5 mg may impair fertility in males of reproductive potential.

4.7 Effects on ability to drive and use machines

Occasionally dizziness or somnolence may occur (see section 4.8). Any affected patients should exercise caution.

4.8 Undesirable effects

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Bone effects
- Increases in cholesterol
- Fatigue and Dizziness

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adjuvant Treatment of Early Breast Cancer

In study, BIG 1-98, the median treatment duration of adjuvant treatment was 60 months and the median duration of follow-up for safety was 96 months for patients receiving Letrozole Tablets 2.5 mg and tamoxifen.

Certain adverse reactions were prospectively specified for analysis (see Table 1), based on the known pharmacologic properties and side effect profiles of the two drugs.

Adverse reactions were analyzed irrespective of whether a symptom was present or absent at baseline. Most adverse reactions reported (approximately 75% of patients who reported AEs) were Grade 1 or Grade 2 applying the Common Toxicity Criteria (CTC) Version 2.0/Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0. Table 1

describes adverse reactions (Grades 1-4 and Grades 3-4) irrespective of relationship to study treatment in the adjuvant trial for the monotherapy arms analysis (safety population).

Table 1: Patients with Adverse Reactions (CTC Grades 1-4,) in the Adjuvant Study – Monotherapy Arms Analysis (Median Follow-up 96 Months; Median Treatment 60 Months)

	Grades 1-4				**Grades 3-4**			
	Letrozole Tablets 2.5 mg		**Tamoxifen**		**Letrozole Tablets 2.5 mg**		**Tamoxifen**	
Adverse Reactions	**N = 2448**		**N = 2447**		**N = 2448**		**N = 2447**	
	n (%)		**n (%)**		**n (%)**		**n (%)**	
Patients with any adverse reaction	2309	(94.3)	2212	(90.4)	636	(26.0)	606	(24.8)
Hypercholesterolemia*	1280	(52.3)	700	(28.6)	11	(0.4)	6	(0.2)
Hot flashes*	819	(33.5)	929	(38.0)	-	-	-	-
Arthralgia/arthritis*	621	(25.4)	504	(20.6)	84	(3.4)	50	(2.0)
Bone fractures1	361	(14.7)	280	(11.4)	-	-	-	-
Night sweats*	356	(14.5)	426	(17.4)	-	-	-	-
Weight increase*	317	(12.9)	378	(15.4)	27	(1.1)	39	(1.6)
Nausea*	284	(11.6)	277	(11.3)	6	(0.2)	9	(0.4)
Bone fractures**2	249	(10.2)	175	(7.2)	-	-	-	-
Fatigue (lethargy, malaise, asthenia)*	235	(9.6)	250	(10.2)	6	(0.2)	7	(0.3)
Myalgia*	221	(9.0)	212	(8.7)	18	(0.7)	14	(0.6)
Vaginal bleeding*	129	(5.3)	320	(13.1)	1	(< 0.1)	8	(0.3)
Edema*	164	(6.7)	160	(6.5)	3	(0.1)	1	(< 0.1)
Weight decrease	140	(5.7)	129	(5.3)	8	(0.3)	5	(0.2)
Osteoporosis**	126	(5.1)	67	(2.7)	10	(0.4)	5	(0.2)
Back pain	125	(5.1)	136	(5.6)	7	(0.3)	11	(0.4)

Bone pain	123	(5.0)	109	(4.5)	6	(0.2)	4	(0.2)
Depression	119	(4.9)	114	(4.7)	16	(0.7)	14	(0.6)
Vaginal irritation*	112	(4.6)	77	(3.1)	2	(< 0.1)	2	(< 0.1)
Headache*	105	(4.3)	94	(3.8)	8	(0.3)	4	(0.2)
Pain in extremity	103	(4.2)	79	(3.2)	6	(0.2)	4	(0.2)
Osteopenia*	87	(3.6)	76	(3.1)	0	-	3	(0.1)
Dizziness/light-headedness*	84	(3.4)	80	(3.3)	1	(< 0.1)	6	(0.2)
Alopecia	83	(3.4)	84	(3.4)	-	-	-	-
Vomiting*	80	(3.3)	80	(3.3)	3	(0.1)	5	(0.2)
Cataract*	49	(2.0)	54	(2.2)	16	(0.7)	17	(0.7)
Constipation*	49	(2.0)	71	(2.9)	3	(0.1)	1	(< 0.1)
Myocardial infarction1	42	(1.7)	28	(1.1)	-	-	-	-
Breast pain*	37	(1.5)	43	(1.8)	1	(< 0.1)	-	-
Anorexia*	20	(0.8)	20	(0.8)	1	(< 0.1)	1	(< 0.1)
Endometrial proliferation disorders*	14	(0.6)	86	(3.5)	0	-	14	(0.6)
Ovarian cyst*	11	(0.4)	18	(0.7)	4	(0.2)	4	(0.2)
Endometrial hyperplasia/cancer**1	11	(0.4)	72	(2.9)	-	-	-	-
Endometrial hyperplasia/cancer**,3	6/1909	(0.3)	57/1943	(2.9)	-	-	-	-
Other endometrial disorders*	2	(< 0.1)	3	(0.1)	0	-	0	-
Myocardial infarction**2	24	(1.0)	12	(0.5)	-	-	-	-
Myocardial ischemia	6	(0.2)	9	(0.4)	-	-	-	-
Cerebrovascular	74	(3.0)	68	(2.8)	-	-	-	-

accident/TIA**1								
Cerebrovascular accident/TIA**2	51	(2.1)	47	(1.9)	-	-	-	-
Angina requiring surgery**1	35	(1.4)	33	(1.3)	-	-	-	-
Angina requiring surgery**2	25	(1.0)	25	(1.0)	-	-	-	-
Thromboembolic event**1	79	(3.2)	113	(4.6)	-	-	-	-
Thromboembolic event**2	51	(2.1)	89	(3.6)	-	-	-	-
Cardiac failure1	39	(1.6)	34	(1.4)	-	-	-	-
Cardiac failure2	27	(1.1)	15	(0.6)	-	-	-	-
Hypertension1	160	(6.5)	175	(7.2)	-	-	-	-
Hypertension2	138	(5.6)	139	(5.7)	-	-	-	-
Other cardiovascular**1	172	(7.0)	174	(7.1)	-	-	-	-
Other cardiovascular**2	120	(4.9)	119	(4.9)	-	-	-	-
Second primary malignancy1	129	(5.3)	150	(6.1)	-	-	-	-
Second primary malignancy2	54	(2.2)	79	(3.2)	-	-	-	-
* Target events pre-specified for analysis ** Events pre-printed on CRF								
[1]At median follow-up of 96 months (i.e. any time after randomization) for Letrozole Tablets 2.5 mg (range up to 144 months) and 95 months for tamoxifen (range up to 143 months) [2]At median treatment duration of 60 months (i.e. during treatment + 30 days after discontinuation of treatment) for Letrozole Tablets 2.5 mg and tamoxifen (range up to 68 months)								

[3]Excluding women who had undergone hysterectomy before study entry
TIA = Transient ischemic attack
Note: Cardiovascular events (including cerebrovascular and thromboembolic events), skeletal and urogenital/endometrial events and second primary malignancies were collected life -long. All of these events were assumed to be of CTC Grade 3 to 5 and were not individually graded

When considering all grades during study treatment, a higher incidence of events was seen for Letrozole Tablets 2.5 mg regarding fractures (10.1% vs 7.1%), myocardial infarctions (1.0% vs 0.5%), and arthralgia (25.2% vs 20.4%) (Letrozole Tablets 2.5 mg vs tamoxifen respectively). A higher incidence was seen for tamoxifen regarding thromboembolic events (2.1% vs 3.6%), endometrial hyperplasia/cancer (0.3% vs 2.9%), and endometrial proliferation disorders (0.3% vs 1.8%) (Letrozole Tablets 2.5 mg vs tamoxifen respectively).

At a median follow-up of 96 months, a higher incidence of events was seen for Letrozole Tablets 2.5 mg (14.7%) than for tamoxifen (11.4%) regarding fractures. A higher incidence was seen for tamoxifen compared to Letrozole Tablets 2.5 mg regarding thromboembolic events (4.6% vs 3.2%), and endometrial hyperplasia or cancer (2.9% vs 0.4%) (tamoxifen vs Letrozole Tablets 2.5 mg, respectively).

Bone Study: Results of a safety trial in 263 postmenopausal women with resected receptor positive early breast cancer in the adjuvant setting comparing the effect on lumbar spine (L2-L4) BMD of adjuvant treatment with letrozole to that with tamoxifen showed at 24 months a median decrease in lumbar spine BMD of 4.1% in the letrozole arm compared to a median increase of 0.3% in the tamoxifen arm (difference = 4.4%) ($P < 0.0001$). No patients with a normal BMD at baseline became osteoporotic over the 2 years and only 1 patient with osteopenia at baseline (T score of -1.9) developed osteoporosis during the treatment period (assessment by central review). The results for total hip BMD were similar, although the differences between the two treatments were less pronounced. During the 2 year period, fractures were reported by 4 of 103 patients (4%) in the letrozole arm, and 6 of 97 patients (6%) in the tamoxifen arm.

Lipid Study: In a safety trial in 263 postmenopausal women with resected receptor positive early breast cancer at 24 months comparing the effects on lipid profiles of adjuvant letrozole to tamoxifen, 12% of patients on letrozole had at least one total cholesterol value of a higher CTCAE grade than at baseline compared with 4% of patients on tamoxifen. In another postapproval randomized, multicenter, open label, study of letrozole vs anastrozole in the adjuvant treatment of postmenopausal women with hormone receptor and node positive breast cancer (FACE, NCT00248170), the median duration of treatment was 60 months for both treatment arms. Table 2 describes adverse reactions (Grades 1-4 and Grades 3-4) irrespective of relationship to study treatment in the adjuvant study (safety population).

Table 2: Adverse Reactions (CTC Grades 1-4), Occurring in at least 5% of Patients in Either Treatment Arm, by Preferred Term (Safety set)

Adverse Reactions	**Letrozole N = 2049 n (%)**	**Anastrozole N = 2062 n (%)**	**Adverse Reactions**	**Letrozole N = 2049 n (%)**
	Grade 3/4 n (%)	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**
tients with at least one AR	628 (30.6)	2049 (100.0)	591 (28.7)	2062 (100.0)
Arthralgia	80 (3.9)	987 (48.2)	69 (3.3)	987 (47.9)
Hot flush	17 (0.8)	666 (32.5)	9 (0.4)	666 (32.3)
Fatigue	8 (0.4)	345 (16.8)	10 (0.5)	343 (16.6)
Osteoporosis	5 (0.2)	223 (10.9)	11 (0.5)	225 (10.9)
Myalgia	16 (0.8)	233 (11.4)	15 (0.7)	212 (10.3)
Back pain	11 (0.5)	212 (10.3)	17 (0.8)	193 (9.4)
Osteopenia	4 (0.2)	203 (9.9)	1 (0.0)	173 (8.4)
Pain in extremity	9 (0.4)	168 (8.2)	3 (0.1)	174 (8.4)
Lymphoedema	5 (0.2)	159 (7.8)	2 (0.1)	179 (8.7)

Insomnia	7 (0.3)	160 (7.8)	3 (0.1)	149 (7.2)
Hypercholesterolaemia	2 (0.1)	155 (7.6)	1 (0.0)	151 (7.3)
Hypertension	25 (1.2)	156 (7.6)	20 (1.0)	149 (7.2)
Depression	16 (0.8)	147 (7.2)	13 (0.6)	137 (6.6)
Bone pain	10 (0.5)	138 (6.7)	9 (0.4)	122 (5.9)
Nausea	6 (0.3)	137 (6.7)	5 (0.2)	152 (7.4)
Headache	3 (0.1)	130 (6.3)	5 (0.2)	168 (8.1)
Alopecia	2 (0.1)	127 (6.2)	0 (0.0)	134 (6.5)
Musculoskeletal pain	6 (0.3)	123 (6.0)	9 (0.4)	147 (7.1)
Radiation skin injury	11 (0.5)	120 (5.9)	6 (0.3)	88 (4.3)
Dyspnoea	16 (0.8)	118 (5.8)	10 (0.5)	96 (4.7)
Cough	1 (0.0)	106 (5.2)	1 (0.0)	120 (5.8)
Musculoskeletal stiffness	2 (0.1)	102 (5.0)	2 (0.1)	84 (4.1)
Dizziness	**2 (0.2)**	**94 (4.6)**	**7 (0.3)**	**109 (5.3)**

The following adverse reactions were also identified in less than 5% of the 2049 patients treated with letrozole and not included in the table: fall, vertigo, hyperbilirubinemia, jaundice, and chest pain.

Extended Adjuvant Treatment of Early Breast Cancer, Median Treatment Duration of 24 Months

In study MA-17, the median duration of extended adjuvant treatment was 24 months and the median duration of follow-up for safety was 28 months for patients receiving Letrozole Tablets 2.5 mg and placebo.

Table 3 describes the adverse reactions occurring at a frequency of at least 5% in any treatment group during treatment. Most adverse reactions reported were Grade 1 and Grade 2 based on the CTC Version 2.0. In the extended adjuvant setting, the reported drug-related

adverse reactions that were significantly different from placebo were hot flashes, arthralgia/arthritis, and myalgia.

Table 3: Adverse Reactions Occurring in at least 5% of Patients in either Treatment Arm

	Number (%) of Patients with Grade 1-4 Adverse Reactions		**Number (%) of Patients with Grade 3-4 Adverse Reactions**	
	Letrozole Tablets 2.5 mg	**Placebo**	**Letrozole Tablets 2.5 mg**	**Placebo**
	N = 2563	**N = 2573**	**N = 2563**	**N = 2573**
Any Adverse Reactions	2232 (87.1)	2174 (84.5)	419 (16.3)	389 (15.1)
Vascular Disorders	1375 (53.6)	1230 (47.8)	59 (2.3)	74 (2.9)
Flushing	1273 (49.7)	1114 (43.3)	3 (0.1)	0
General Disorders	1154 (45)	1090 (42.4)	30 (1.2)	28 (1.1)
Asthenia	862 (33.6)	826 (32.1)	16 (0.6)	7 (0.3)
Edema NOS	471 (18.4)	416 (16.2)	4 (0.2)	3 (0.1)
Musculoskeletal Disorders	978 (38.2)	836 (32.5)	71 (2.8)	50 (1.9)
Arthralgia	565 (22)	465 (18.1)	25 (1)	20 (0.8)
Arthritis NOS	173 (6.7)	124 (4.8)	10 (0.4)	5 (0.2)
Myalgia	171 (6.7)	122 (4.7)	8 (0.3)	6 (0.2)
Back Pain	129 (5)	112 (4.4)	8 (0.3)	7 (0.3)
Nervous System Disorders	863 (33.7)	819 (31.8)	65 (2.5)	58 (2.3)
Headache	516 (20.1)	508 (19.7)	18 (0.7)	17 (0.7)
Dizziness	363 (14.2)	342 (13.3)	9 (0.4)	6 (0.2)
Skin Disorders	830 (32.4)	787 (30.6)	17 (0.7)	16 (0.6)
Sweating Increased	619 (24.2)	577 (22.4)	1 (< 0.1)	0

Gastrointestinal Disorders	725 (28.3)	731 (28.4)	43 (1.7)	42 (1.6)
Constipation	290 (11.3)	304 (11.8)	6 (0.2)	2 (< 0.1)
Nausea	221 (8.6)	212 (8.2)	3 (0.1)	10 (0.4)
Diarrhea NOS	128 (5)	143 (5.6)	12 (0.5)	8 (0.3)
Metabolic Disorders	551 (21.5)	537 (20.9)	24 (0.9)	32 (1.2)
Hypercholesterolemia	401 (15.6)	398 (15.5)	2 (< 0.1)	5 (0.2)
Reproductive Disorders	303 (11.8)	357 (13.9)	9 (0.4)	8 (0.3)
Vaginal Hemorrhage	123 (4.8)	171 (6.6)	2 (< 0.1)	5 (0.2)
Vulvovaginal Dryness	137 (5.3)	127 (4.9)	0	0
Psychiatric Disorders	320 (12.5)	276 (10.7)	21 (0.8)	16 (0.6)
Insomnia	149 (5.8)	120 (4.7)	2 (< 0.1)	2 (< 0.1)
Respiratory Disorders	279 (10.9)	260 (10.1)	30 (1.2)	28 (1.1)
Dyspnea	140 (5.5)	137 (5.3)	21 (0.8)	18 (0.7)
Investigations	184 (7.2)	147 (5.7)	13 (0.5)	13 (0.5)
Infections and Infestations	166 (6.5)	163 (6.3)	40 (1.6)	33 (1.3)
Renal Disorders	130 (5.1)	100 (3.9)	12 (0.5)	6 (0.2)

Based on a median follow-up of patients for 28 months,the incidence of clinical fractures from the core randomized study in patients who received Letrozole Tablets 2.5 mg was 5.9% (152) and placebo was 5.5% (142). The incidence of self-reported osteoporosis was higher in patients who received Letrozole Tablets 2.5 mg 6.9% (176) than in patients who received

placebo 5.5% (141). Bisphosphonates were administered to 21.1% of the patients who received Letrozole Tablets 2.5 mg and 18.7% of the patients who received placebo.

The incidence of cardiovascular ischemic events from the core randomized study was comparable between patients who received Letrozole Tablets 2.5 mg 6.8% (175) and placebo 6.5% (167).

A patient-reported measure that captures treatment impact on important symptoms associated with estrogen deficiency demonstrated a difference in favor of placebo for vasomotor and sexual symptom domains.

Bone Substudy:

Lipid Substudy: In the extended adjuvant setting, based on a median duration of follow-up of 62 months, there was no significant difference between Letrozole Tablets 2.5 mg and placebo in total cholesterol or in any lipid fraction at any time over 5 years. Use of lipid lowering drugs or dietary management of elevated lipids was allowed.

Updated Analysis, Extended Adjuvant Treatment of Early Breast Cancer, Median Treatment Duration of 60 Months

The extended adjuvant treatment trial (MA-17) was unblinded early . At the updated (final analysis), overall the side effects seen were consistent to those seen at a median treatment duration of 24 months.

During treatment or within 30 days of stopping treatment (median duration of treatment 60 months) a higher rate of fractures was observed for Letrozole Tablets 2.5 mg (10.4%) compared to placebo (5.8%), as also a higher rate of osteoporosis (Letrozole Tablets 2.5 mg 12.2% vs placebo 6.4%).

Based on 62 months median duration of follow-up in the randomized letrozole arm in the safety population the incidence of new fractures at any time after randomization was 13.3% for letrozole and 7.8% for placebo. The incidence of new osteoporosis was 14.5% for letrozole and 7.8% for placebo.

During treatment or within 30 days of stopping treatment (median duration of treatment 60 months), the incidence of cardiovascular events was 9.8% for Letrozole Tablets 2.5 mg and 7.0% for placebo.

Based on 62 months median duration of follow-up in the randomized letrozole arm in the safety population the incidence of cardiovascular disease at any time after randomization was 14.4% for letrozole and 9.8% for placebo.

Lipid substudy: In the extended adjuvant setting (MA-17), based on a median duration of follow-up of 62 months, there was no significant difference between Letrozole Tablets 2.5 mg and placebo in total cholesterol or in any lipid fraction over 5 years. Use of lipid lowering drugs or dietary management of elevated lipids was allowed.

First-Line Treatment of Advanced Breast Cancer

In study P025 a total of 455 patients were treated for a median time of exposure of 11 months in the Letrozole Tablets 2.5 mg arm (median 6 months in the tamoxifen arm). The incidence of adverse reactions was similar for Letrozole Tablets 2.5 mg and tamoxifen. The most frequently reported adverse reactions were bone pain, hot flushes, back pain, nausea, arthralgia and dyspnea. Discontinuations for adverse reactions other than progression of tumor occurred in 10/455 (2%) of patients on Letrozole Tablets 2.5 mg and in 15/455 (3%) of patients on tamoxifen.

Adverse reactions that were reported in at least 5% of the patients treated with Letrozole Tablets 2.5 mg 2.5 mg or tamoxifen 20 mg in the first-line treatment study are shown in Table 4.

Table 4: Adverse Reactions Occurring in at least 5% of Patients in either Treatment Arm

Adverse	**Letrozole Tablets 2.5 mg**	**Tamoxifen**
Reactions	**2.5 mg**	**20 mg**
	(N = 455)	**(N = 455)**
	%	**%**
General Disorders		

Fatigue	13	13
Chest Pain	8	9
Edema Peripheral	5	6
Pain NOS	5	7
Weakness	6	4
Investigations		
Weight Decreased	7	5
Vascular Disorders		
Hot Flushes	19	16
Hypertension	8	4
Gastrointestinal Disorders		
Nausea	17	17
Constipation	10	11
Diarrhea	8	4
Vomiting	7	8
Infections/Infestations		
Influenza	6	4
Urinary Tract Infection NOS	6	3
Injury, Poisoning and Procedural Complications		
Post-Mastectomy Lymphedema	7	7
Metabolism and Nutrition Disorders		
Anorexia	4	6
Musculoskeletal and Connective Tissue Disorders		

Bone Pain	22	21
Back Pain	18	19
Arthralgia	16	15
Pain in Limb	10	8
Nervous System Disorders		
Headache NOS	8	7
Psychiatric Disorders		
Insomnia	7	4
Reproductive System and Breast Disorders		
Breast Pain	7	7
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	18	17
Cough	13	13
Chest Wall Pain	6	6

Other less frequent (less than or equal to 2%) adverse reactions considered consequential for both treatment groups, included peripheral thromboembolic events, cardiovascular events, and cerebrovascular events. Peripheral thromboembolic events included venous thrombosis, thrombophlebitis, portal vein thrombosis and pulmonary embolism. Cardiovascular events included angina, myocardial infarction, myocardial ischemia, and coronary heart disease. Cerebrovascular events included transient ischemic attacks, thrombotic or hemorrhagic strokes and development of hemiparesis.

Second-Line Treatment of Advanced Breast Cancer

Study discontinuations in the megestrol acetate comparison study (AR/BC2) for adverse reactions other than progression of tumor were 5/188 (2.7%) on Letrozole Tablets 2.5 mg 0.5 mg, in 4/174 (2.3%) on Letrozole Tablets 2.5 mg 2.5 mg, and in 15/190 (7.9%) on megestrol acetate. There were fewer thromboembolic events at both Letrozole Tablets 2.5 mg doses than on the megestrol acetate arm (0.6% vs 4.7%). There was also less vaginal bleeding

(0.3% vs 3.2%) on Letrozole Tablets 2.5 mg than on megestrol acetate. In the aminoglutethimide comparison study (AR/BC3), discontinuations for reasons other than progression occurred in 6/193 (3.1%) on 0.5 mg Letrozole Tablets 2.5 mg, 7/185 (3.8%) on 2.5 mg Letrozole Tablets 2.5 mg, and 7/178 (3.9%) of patients on aminoglutethimide.

Comparisons of the incidence of adverse reactions revealed no significant differences between the high and low dose Letrozole Tablets 2.5 mg groups in either study. Most of the adverse reactions observed in all treatment groups were mild to moderate in severity and it was generally not possible to distinguish adverse reactions due to treatment from the consequences of the patient's metastatic breast cancer, the effects of estrogen deprivation, or intercurrent illness.

Adverse reactions that were reported in at least 5% of the patients treated with Letrozole Tablets 2.5 mg 0.5 mg, Letrozole Tablets 2.5 mg 2.5 mg, megestrol acetate, or aminoglutethimide in the two controlled trials AR/BC2 and AR/BC3 are shown in Table 5.

Table 5: Adverse Reactions Occurring at a Frequency of at Least 5% of Patients in Either Treatment Arm

Adverse	**Pooled**	**Pooled**	**Megestrol**	
Reactions	**Letrozole Tablets 2.5 mg**	**Letrozole Tablets 2.5 mg**	**Acetate**	**Aminoglutethimide**
	2.5 mg	**0.5 mg**	**160 mg**	**500 mg**
	(N = 359)	**(N = 380)**	**(N = 189)**	**(N = 178)**
	%	**%**	**%**	**%**
Body as a Whole				
Chest Pain	6	3	7	3
Peripheral Edema1	5	5	8	3
Asthenia	4	5	4	5
Weight Increase	2	2	9	3
Cardiovascular				

Hypertension	5	7	5	6
Digestive System				
Nausea	13	15	9	14
Vomiting	7	7	5	9
Constipation	6	7	9	7
Diarrhea	6	5	3	4
Pain-Abdominal	6	5	9	8
Anorexia	5	3	5	5
Dyspepsia	3	4	6	5
Infections/Infestations				
Viral Infection	6	5	6	3
Lab Abnormality				
Hypercholesterolemia	3	3	0	6
Musculoskeletal System				
Musculoskeletal2	21	22	30	14
Arthralgia	8	8	8	3
Nervous System				
Headache	9	12	9	7
Somnolence	3	2	2	9
Dizziness	3	5	7	3
Respiratory System				
Dyspnea	7	9	16	5
Coughing	6	5	7	5
Skin and Appendages				
Hot Flushes	6	5	4	3
Rash3	5	4	3	12
Pruritus	1	2	5	3

[1]Includes peripheral edema, leg edema, dependent edema, edema
[2]Includes musculoskeletal pain, skeletal pain, back pain, arm pain, leg pain
[3]Includes rash, erythematous rash, maculopapular rash, psoriasiform rash, vesicular rash

Other less frequent (less than 5%) adverse reactions considered consequential and reported in at least 3 patients treated with Letrozole Tablets 2.5 mg, included hypercalcemia, fracture, depression, anxiety, pleural effusion, alopecia, increased sweating and vertigo.

First and Second-Line Treatment of Advanced Breast Cancer

In the combined analysis of the first- and second-line metastatic trials and postmarketing experiences other adverse reactions that were reported were cataract, eye irritation, palpitations, cardiac failure, tachycardia, dysesthesia (including hypesthesia/paresthesia), arterial thrombosis, memory impairment, irritability, nervousness, urticaria, increased urinary frequency, leukopenia, stomatitis cancer pain, pyrexia, vaginal discharge, appetite increase, dryness of skin and mucosa (including dry mouth), and disturbances of taste and thirst.

4.9 Overdose

Isolated cases of Letrozole Tablets 2.5 mg overdose have been reported. In these instances, the highest single dose ingested was 62.5 mg or 25 tablets. While no serious adverse reactions were reported in these cases, because of the limited data available, no firm recommendations for treatment can be made. However, emesis could be induced if the patient is alert. In general, supportive care and frequent monitoring of vital signs are also appropriate. In single-dose studies, the highest dose used was 30 mg, which was well tolerated; in multiple-dose trials, the largest dose of 10 mg was well tolerated.

Lethality was observed in mice and rats following single oral doses that were equal to or greater than 2,000 mg/kg (about 4,000 to 8,000 times the daily maximum recommended human dose on a mg/m^2 basis); death was associated with reduced motor activity, ataxia and dyspnea. Lethality was observed in cats following single IV doses that were equal to or greater than 10 mg/kg (about 50 times the daily maximum recommended human dose on a mg/m^2 basis); death was preceded by depressed blood pressure and arrhythmias.

5. Pharmacological properties

5.1 Pharmacodynamic properties

In postmenopausal patients with advanced breast cancer, daily doses of 0.1 mg to 5 mg Letrozole Tablets 2.5 mg (letrozole) suppress plasma concentrations of estradiol, estrone, and estrone sulfate by 75% to 95% from baseline with maximal suppression achieved within two-three days. Suppression is dose-related, with doses of 0.5 mg and higher giving many values of estrone and estrone sulfate that were below the limit of detection in the assays. Estrogen suppression was maintained throughout treatment in all patients treated at 0.5 mg or higher.

Letrozole is highly specific in inhibiting aromatase activity. There is no impairment of adrenal steroidogenesis. No clinically-relevant changes were found in the plasma concentrations of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxy-progesterone, ACTH or in plasma renin activity among postmenopausal patients treated with a daily dose of Letrozole Tablets 2.5 mg 0.1 mg to 5 mg. The ACTH stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0.1, 0.25, 0.5, 1, 2.5, and 5 mg did not indicate any attenuation of aldosterone or cortisol production. Glucocorticoid or mineralocorticoid supplementation is, therefore, not necessary.

No changes were noted in plasma concentrations of androgens (androstenedione and testosterone) among healthy postmenopausal women after 0.1, 0.5, and 2.5 mg single doses of Letrozole Tablets 2.5 mg or in plasma concentrations of androstenedione among postmenopausal patients treated with daily doses of 0.1 mg to 5 mg. This indicates that the blockade of estrogen biosynthesis does not lead to accumulation of androgenic precursors. Plasma levels of LH and FSH were not affected by letrozole in patients, nor was thyroid function as evaluated by TSH levels, T3 uptake, and T4 levels.

<u>Mechanism of action</u>

The growth of some cancers of the breast is stimulated or maintained by estrogens. Treatment of breast cancer thought to be hormonally responsive (i.e., estrogen and/or progesterone receptor positive or receptor unknown) has included a variety of efforts to decrease estrogen levels (ovariectomy, adrenalectomy, hypophysectomy) or inhibit estrogen

effects (antiestrogens and progestational agents). These interventions lead to decreased tumor mass or delayed progression of tumor growth in some women.

In postmenopausal women, estrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens (primarily androstenedione and testosterone) to estrone and estradiol. The suppression of estrogen biosynthesis in peripheral tissues and in the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme.

Letrozole is a nonsteroidal competitive inhibitor of the aromatase enzyme system; it inhibits the conversion of androgens to estrogens. In adult nontumor- and tumor-bearing female animals, letrozole is as effective as ovariectomy in reducing uterine weight, elevating serum LH, and causing the regression of estrogen-dependent tumors. In contrast to ovariectomy, treatment with letrozole does not lead to an increase in serum FSH. Letrozole selectively inhibits gonadal steroidogenesis but has no significant effect on adrenal mineralocorticoid or glucocorticoid synthesis.

Letrozole inhibits the aromatase enzyme by competitively binding to the heme of the cytochrome P450 subunit of the enzyme, resulting in a reduction of estrogen biosynthesis in all tissues. Treatment of women with letrozole significantly lowers serum estrone, estradiol and estrone sulfate and has not been shown to significantly affect adrenal corticosteroid synthesis, aldosterone synthesis, or synthesis of thyroid hormones.

5.2 Pharmacokinetic properties

Absorption and Distribution: Letrozole is rapidly and completely absorbed from the gastrointestinal tract and absorption is not affected by food. It is metabolized slowly to an inactive metabolite whose glucuronide conjugate is excreted renally, representing the major clearance pathway. About 90% of radiolabeled letrozole is recovered in urine. Letrozole's terminal elimination half-life is about 2 days and steady-state plasma concentration after daily 2.5 mg dosing is reached in 2-6 weeks. Plasma concentrations at steady state are 1.5 to 2 times higher than 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. These steady-state levels are maintained over extended periods, however, and continuous

accumulation of letrozole does not occur. Letrozole is weakly protein bound and has a large volume of distribution (approximately 1.9 L/kg).

Elimination

Metabolism and Excretion: Metabolism to a pharmacologically-inactive carbinol metabolite (4,4'-methanol-bisbenzonitrile) and renal excretion of the glucuronide conjugate of this metabolite is the major pathway of letrozole clearance. Of the radiolabel recovered in urine, at least 75% was the glucuronide of the carbinol metabolite, about 9% was two unidentified metabolites, and 6% was unchanged letrozole.

In human microsomes with specific CYP isozyme activity, CYP3A4 metabolized letrozole to the carbinol metabolite while CYP2A6 formed both this metabolite and its ketone analog. In human liver microsomes, letrozole inhibited CYP2A6 and CYP2C19, however, the clinical significance of these findings is unknown.

Specific Populations

Pediatric, Geriatric and Race: In the study populations (adults ranging in age from 35 to greater than 80 years), no change in pharmacokinetic parameters was observed with increasing age. Differences in letrozole pharmacokinetics between adult and pediatric populations have not been studied. Differences in letrozole pharmacokinetics due to race have not been studied.

Renal Impairment: In a study of volunteers with varying renal function (24-hour creatinine clearance: 9 to 116 mL/min), no effect of renal function on the pharmacokinetics of single doses of 2.5 mg of Letrozole Tablets 2.5 mg was found. In addition, in a study (AR/BC2) of 347 patients with advanced breast cancer, about half of whom received 2.5 mg Letrozole Tablets 2.5 mg and half 0.5 mg Letrozole Tablets 2.5 mg, renal impairment (calculated creatinine clearance: 20 to 50 mL/min) did not affect steady-state plasma letrozole concentrations.

Hepatic Impairment: In a study of subjects with mild to moderate non-metastatic hepatic dysfunction (e.g., cirrhosis, Child-Pugh classification A and B), the mean area under curve (AUC) values of the volunteers with moderate hepatic impairment were 37% higher than in normal subjects, but still within the range seen in subjects without impaired function.

In a pharmacokinetic study, subjects with liver cirrhosis and severe hepatic impairment (Child-Pugh classification C, which included bilirubins about 2-11 times ULN with minimal to severe ascites) had two-fold increase in exposure (AUC) and 47% reduction in systemic clearance. Breast cancer patients with severe hepatic impairment are thus expected to be exposed to higher levels of letrozole than patients with normal liver function receiving similar doses of this drug.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose monohydrate (Pharmatose 200 M)

Povidone (Plasdone K-29/32)

Croscarmellose Sodium (Ac-Di-Sol)

Magnesium stearate

Opadry Yellow 03B82401

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 Years

6.4 Special precautions for storage

Store below 30°C and protect from moisture.

6.5 Nature and contents of container

30’s HDPE Container

6.6 Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

7.1 Name and Address of Manufacturer

(Company) Name : Hetero Labs Limited (Unit-VI)

Address : Unit – VI, Sy.No.440 & 441,
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Country : India

7.2 Name and Address of Principal

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Country : INDIA

Telephone : 0091-040-23704923/24

8. REGISTRATION NUMBER

Not applicable

9. DATE OF PUBLICATION OF THIS PACKAGE INSERT

Not applicable