Summary of Product Characteristic

1. Name of the Medicinal Product:

Letrozole tablets 2.5mg

2. Quality and Quantitative Composition:

2.1 Qualitative Declaration

Each film coated tablet contains:
Letrozole.....2.5mg
Excipients.....q.s.
Colour : Yellow oxide of Iron & Titanium dioxide

2.2 Quantitative Declaration

Composition:

Components	Amount /Unit (mg)	Reference
Letrozole	2.500	USP (NF)
Lactose Monohydrate	60.000	USP (NF)
Maize Starch Powder	14.030	Ph Eur (BP)
Micro Crystalline Cellulose	18.000	Ph Eur (BP)
Povidone-K 30	2.000	USP (NF)
Purified Water	Q.S.	Ph Eur (BP)
Magnesium Stearate	2.000	Ph Eur (BP)
Sodium Starch Glycolate	6.000	USP (NF)
Colloidal Silicone Dioxide	0.500	USP (NF)
Adnova Coat	2.876	In-House
Isopropyl Alcohol	19.782	Ph Eur (BP)
Di-chloromethane	50.463	Ph Eur (BP)
Lake Of Iron oxide Yellow	0.094	In-House

3. Pharmaceutical Form:

Tablet (Oral use)

4. Clinical Particulars:

4.1 Therapeutic indications

- Adjuvant treatment of post-menopausal women with hormone receptor positive early breast cancer.
- Extended adjuvant treatment of hormone-dependent early breast cancer in post-menopausal women who have received prior standard adjuvant tamoxifen therapy for 5 years.
- First-line treatment in post-menopausal women with hormone-dependent advanced breast cancer.
- Advanced breast cancer in women with natural or artificially-induced postmenopausal status after relapse or disease progression, who have previously been treated with anti-oestrogens.

Summary of Product Characteristic

4.2 Posology and method of administration

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

In the adjuvant setting, it is recommended to treat for 5 years or until tumour relapse occurs. In the adjuvant setting, clinical experience is available for 2 years (median duration of treatment was 25 months).

In the extended adjuvant setting, clinical experience is available for 4 years (median duration of treatment).

In patients with advanced or metastatic disease, treatment with letrozole should continue until tumour progression is evident.

Children
Not applicable.

Patients with hepatic and/or renal impairment
No dosage adjustment is required for patients with renal insufficiency with creatinine clearance greater than 30 ml/min. Insufficient data are available in cases of renal insufficiency with creatinine clearance lower than 30 ml/min or in patients with severe hepatic insufficiency

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Pre-menopausal endocrine status; pregnancy; lactation

4.4 Special warning and precautions for use

In patients whose post-menopausal status seems unclear, LH, FSH and/or oestradiol levels must be assessed before initiating treatment in order to clearly establish menopausal status.

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

Hepatic impairment
Letrozole has only been studied in a limited number of non-metastatic patients with varying degrees of hepatic function: mild to moderate, and severe hepatic insufficiency. In non-cancer male volunteers with severe hepatic impairment (liver cirrhosis and Child-Pugh score C), systemic exposure and terminal halflife were increased 2-3-fold compared to healthy volunteers.

Thus, letrozole should be administered with caution and after careful consideration of the potential risk/benefit to such patients.

Bone Effects
Letrozole is a potent oestrogen-lowering agent. In the adjuvant and extended adjuvant setting the median follow-up duration of 30 and 49 months respectively is insufficient to fully assess the fracture risk associated with long-term use of letrozole. 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 by bone densitometry prior to the commencement of adjuvant and extended adjuvant treatment and be monitored for development of osteoporosis during and following treatment with letrozole. Treatment or prophylaxis for osteoporosis should be initiated as appropriate and carefully monitored.

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

4.5 Interaction with other medicinal products and other forms of interaction

Clinical interaction studies with cimetidine and warfarin indicated that the co-administration of letrozole with these agents does not result in clinically significant interactions.

Additionally, a review of the clinical trial database indicated no evidence of clinically relevant interactions with other commonly prescribed agents.

There is no clinical experience to date on the use of letrozole in combination with other anti-cancer agents.

In vitro, letrozole inhibits the cytochrome P450 isoenzymes 2A6 and, moderately, 2C19. Thus, caution should be used in the concomitant administration of agents whose disposition is mainly dependent on these isoenzymes and whose therapeutic index is narrow.

4.6 Pregnancy and lactation

Women of peri-menopausal status or child-bearing potential
The physician needs to discuss the necessity of a pregnancy test before initiating letrozole and of adequate contraception with women who have the potential to become pregnant (i.e. women who are peri-menopausal or who recently became post-menopausal) until their post-menopausal status is fully established.

Pregnancy:
Letrozole is contraindicated during pregnancy.

Lactation
Letrozole is contraindicated during lactation.

4.7 Effects on ability to drive and use machine
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

Letrozole was generally well tolerated across all studies as first-line and

second-line treatment for advanced breast cancer and as adjuvant treatment of early breast cancer. Up to approximately one third of the patients treated with letrozole in the metastatic setting, up to approximately 70-75% of the patients in the adjuvant setting (both letrozole and tamoxifen arms), and up to approximately 40% of the patients treated in the extended adjuvant setting (both letrozole and placebo arms) experienced adverse reactions. Generally, the observed adverse reactions are mainly mild or moderate in nature. Most adverse reactions can be attributed to normal pharmacological consequences of oestrogen deprivation (e.g. hot flushes).

The most frequently reported adverse reactions in the clinical studies were hot flushes, arthralgia, nausea and fatigue. Many adverse reactions can be attributed to the normal pharmacological consequences of oestrogen deprivation (e.g. hot flushes, alopecia and vaginal bleeding).

After standard adjuvant tamoxifen, based on median follow-up of 28 months, the following adverse events irrespective of causality were reported significantly more often with letrozole than with placebo: hot flushes (50.7% vs. 44.3%), arthralgia/arthritis (28.5% vs. 23.2%) and myalgia (10.2% vs. 7.0%). The majority of these adverse events were observed during the first year of treatment. There was a higher but non-significant incidence of osteoporosis and bone fractures in patients who received letrozole than in patients who received placebo (7.5% vs. 6.3% and 6.7% vs. 5.9%, respectively).

In an updated analysis in the extended adjuvant setting conducted at a median treatment duration of 47 months for letrozole and 28 months for placebo, the following adverse events irrespective of causality were reported significantly more often with letrozole than with placebo: hot flushes (60.3% vs. 52.6%), arthralgia/arthritis (37.9% vs. 26.8%) and myalgia (15.8% vs. 8.9%). The majority of these adverse events were observed during the first year of treatment. In the patients in placebo arm who switched to Letrozole, a similar pattern of general events was observed. There was a higher incidence of osteoporosis and bone fractures, any time after randomisation, in patients who received Letrozole than in patients who received placebo (12.3% vs. 7.4% and 10.9% vs. 7.2%, respectively). In patients who switched to letrozole, newly diagnosed osteoporosis, any time after switching, was reported in 3.6% of patients while fracture were reported in 5.1% of patients any time after switching.

In the adjuvant setting, irrespective of causality, the following adverse events occurred any time after randomisation in the letrozole and tamoxifen groups respectively: thromboembolic events (1.5% vs. 3.2%, $P<0.001$), angina pectoris (0.8% vs. 0.8%,), myocardial infarction (0.7% vs. 0.4%) and cardiac failure (0.9% vs. 0.4%, $P=0.006$).

The following adverse drug reactions, listed in Table 1, were reported from clinical studies and from post marketing experience with Letrozole.

Table 1

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: 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
Neoplasms, benign, malignant and unspecified (including cysts and polyps)	
Uncommon:	Tumour pain (not applicable in the adjuvant and extended adjuvant setting)
Blood and the lymphatic system disorders	
Uncommon:	Leucopenia
Metabolism and nutrition disorders	
Common:	Anorexia, appetite increase, hypercholesterolaemia
Uncommon:	General oedema
Psychiatric disorders	
Common:	Depression
Uncommon:	Anxiety including nervousness, irritability
Nervous system disorders	
Common:	Headache, dizziness
Uncommon:	Somnolence, insomnia, memory impairment, dysaesthesia including paresthesia, hypoaesthesia, taste disturbance, cerebrovascular accident
Eye disorders	
Uncommon:	Cataract, eye irritation, blurred vision
Cardiac disorders	
Uncommon:	Palpitations, tachycardia
Vascular disorders	
Uncommon:	Thrombophlebitis including superficial and deep thrombophlebitis, hypertension, ischaemic cardiac events

Rare: Pulmonary embolism, arterial thrombosis, cerebrovascular infarction *Respiratory, thoracic and mediastinal disorders*

Uncommon:	Dyspnoea, cough
Gastrointestinal disorders	
Common:	Nausea, vomiting, dyspepsia, constipation, diarrhoea
Uncommon:	Abdominal pain, stomatitis, dry mouth
Hepatobiliary disorders	
Uncommon:	Increased hepatic enzymes
Not known:	Hepatitis
Skin and subcutaneous tissue disorders	

Very	Increased sweating
Common	Alopecia, rash including erythematous, maculopapular, psoriaform and vesicular rash
Uncommon:	Pruritus, dry skin, urticaria
Not known:	Anaphylactic reaction, angioedema, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders	
Very	Arthralgia
Common:	Myalgia, bone pain, osteoporosis, bone fractures
Uncommon:	Arthritis
Renal and urinary disorders	
Uncommon:	Increased urinary frequency
Reproductive system and breast disorders	
Uncommon:	Vaginal bleeding, vaginal discharge, vaginal dryness, breast
General disorders and administration site conditions	
Very	Hot flushes, fatigue including asthenia
Common:	Malaise, peripheral oedema
Uncommon:	Pyrexia, mucosal dryness, thirst
Investigations	
Common:	Weight increase
Uncommon:	Weight loss

4.9 Overdose and treatment

Isolated cases of overdose with letrozole have been reported.
No specific treatment for overdosage is known; treatment should be symptomatic and supportive

5. Pharmacological Properties:

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group
Enzyme inhibitor. Non-steroidal aromatase inhibitor (inhibitor of oestrogen biosynthesis); antineoplastic agent
ATC code: L02B G04

In postmenopausal patients with advanced breast cancer, daily doses of 0.1 mg to 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 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 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.

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'-methanolbisbenzonitrile) 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 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 and half 0.5 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.

5.3 Preclinical safety Data

A conventional carcinogenesis study in mice at doses of 0.6 to 60 mg/kg/day (about 1 to 100 times the daily maximum recommended human dose on a mg/m2 basis) administered by oral gavage for up to 2 years revealed a dose-related increase in the incidence of benign ovarian stromal tumors. The incidence of combined hepatocellular adenoma and carcinoma showed a significant trend in females when the high dose group was excluded due to low survival. In a separate study, plasma AUC0-12hr levels in mice at 60 mg/kg/day were 55 times higher than the AUC0-24hr level in breast cancer patients at the recommended dose. The carcinogenicity study in rats at oral doses of 0.1 to 10 mg/kg/day (about 0.4 to 40 times the daily maximum recommended human dose on a mg/m2 basis) for up to 2 years also produced an increase in the incidence of benign ovarian stromal tumors at 10 mg/kg/day. Ovarian hyperplasia was observed in females at doses equal to or greater than 0.1 mg/kg/day. At 10 mg/kg/day, plasma AUC0-24hr levels in rats were 80 times higher than the level in breast cancer patients at the recommended dose. The benign ovarian stromal tumors observed in mice and rats were considered to be related to the pharmacological inhibition of estrogen synthesis and may be due to increased luteinizing hormone resulting from the decrease in circulating estrogen.

Letrozole was not mutagenic in *in vitro* tests (Ames and E.coli bacterial tests) but was observed to be a potential clastogen in *in vitro* assays (CHO K1 and CCL 61 Chinese hamster ovary cells). Letrozole was not clastogenic *in vivo* (micronucleus test in rats).

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 $\geq$ 0.03 mg/kg/day (approximately 0.1 times the maximum recommended human dose on a mg/m2 basis). In repeat-dose toxicity studies, administration of letrozole caused sexual inactivity in females and atrophy of the reproductive tract in males and females at doses of 0.6, 0.1 and 0.03 mg/kg in mice, rats and dogs, respectively (approximately 1, 0.4 and 0.4 times the daily maximum recommended human dose on a mg/m2 basis, respectively).

Summary of Product Characteristic

6. Pharmaceutical Particulars:

6.1 List of excipients

Lactose Monohydrate, Maize Starch Powder, Micro Crystalline Cellulose, Povidone K-30, Purified Water, Magnesium Stearate, Sodium Starch Glycolate, Colloidal Silicone Dioxide, Adnova Coat, Isopropyl Alcohol, Di-chloromethane, Lake Of Iron oxide Yellow.

6.2 Incompatibilities

Not known

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C, protected from light & moisture.

6.5 Nature and contents of container

10 tablets packed in a Alu-PVC blister and 1 such blister is packed in a printed carton. Such cartons packed in export worthy shipper.

7. Marketing Authorization Holder:

NAME: Adnova Healthcare Pvt. Ltd.
ADDRESS: 156/157A, Siddhi Industrial Infrastructure Park,
Waghodia, Vadodara, 391 760 Gujarat, India
Ph.No. + 91 9974949949
Email: adnovahealthcare@gmail.com

8. Marketing Authorization Number (s):

Product license / registration Number (s)

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9. Manufacturer Name:

NAME: Adnova Healthcare Pvt. Ltd.
ADDRESS: 156/157A, Siddhi Industrial Infrastructure Park,
Waghodia, Vadodara, 391 760 Gujarat, India
Ph.No. + 91 9974949949
Email: adnovahealthcare@gmail.com

10. Date of first authorization/renewal of the authorization:

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11. Date of revision of the text:

April 2024