Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Letrozole 2.5 mg Film-coated Tablets

PL 00289/1168

UK/H/1570/01/DC

TEVA UK Limited

Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted TEVA UK Limited a Marketing Authorisation (licence) for the medicinal product Letrozole 2.5 mg Film-coated Tablets (product licence number: 00289/1168). This medicine is available on prescription only.

Letrozole 2.5 mg Film-coated Tablets belong to a group of medicines known as the aromatase inhibitors. Aromatase inhibitors are a type of hormonal (endocrine) breast cancer treatment.

Letrozole is used to prevent breast cancer coming back. It can be used as a first treatment after breast surgery or following 5 years of treatment with tamoxifen. Letrozole is also used to prevent breast tumors spreading to other parts of the body in patients with advanced breast cancer.

Letrozole should only be used for oestrogen receptor positive breast cancer and in women after menopause.

The data submitted in support of this application for Letrozole 2.5 mg Film-coated Tablets raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Information about decentralised procedure

Name of the product in the Reference Member State	Letrozole 2.5 mg Film-coated Tablets
Type of application (Eudratrack details)	Level 1 Abridged Level 2 Initial Level 3 10.1 Level 4 Chemical substance Level 5 Prescription only
Name of the active substance (INN)	Letrozole
Pharmacotherapeutic classification (ATC code)	Enzyme Inhibitors (L02B G04)
Pharmaceutical form and strength	2.5 mg film coated tablets
Reference numbers for the decentralised Procedure	UK/H/1570/01/DC
Reference Member State	United Kingdom
Member States concerned	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, NL, NO, PL, PT, RO, SE, SI
Date of start of the procedure	06 August 2008
End date of decentralised procedure	18 December 2009
Marketing Authorisation Number	PL 00289/1168
Name and address of the authorisation holder	TEVA UK Limited Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG United Kingdom

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Letrozole 2.5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5 mg letrozole.

Excipients

Each film-coated tablet contains 60.42 mg lactose and 0.02 mg tartrazine aluminium lake (E102).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Dark yellow, standard convex round, film-coated tablet debossed with "93" on one side and "B1" on the other side.

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 post-menopausal status after relapse or disease progression, who have previously been treated with anti-oestrogens.

Efficacy has not been demonstrated in patients with hormone receptor-negative breast cancer.

4.2 Posology and method of administration

Adults 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 (see sections 4.4 and 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Pre-menopausal endocrine status; pregnancy; lactation (see sections 4.6 and 5.3).

4.4 Special warnings 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 half-life 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 (see section 5.2).

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/of 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 (see section 4.8).

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

This medicinal product contains tartrazine aluminium lake (E102) and may cause allergic reactions.

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 (see sections 4.4 and 5.3).

Pregnancy

Letrozole is contraindicated during pregnancy (see sections 4.3 and 5.3).

Lactation

Letrozole is contraindicated during lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

Since fatigue and dizziness have been observed with the use of letrozole and somnolence has been reported uncommonly, caution is advised when driving or using machines.

4.8 Undesirable effects

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 a 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 the 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 fractures 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 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 paraesthesia, 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 common:	Increased sweating
Common:	Alopecia, rash including erythematous, maculopapular, psoriasiform and vesicular rash
Uncommon:	Pruritus, dry skin, urticaria

Not known:	Anaphylactic reaction, angioedema, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders	
Very common:	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 pain
General disorders and administration site conditions	
Very common:	Hot flushes, fatigue including asthenia
Common:	Malaise, peripheral oedema
Uncommon:	Pyrexia, mucosal dryness, thirst
Investigations	
Common:	Weight increase
Uncommon:	Weight loss

4.9 Overdose

Isolated cases of overdose with letrozole have been reported.

No specific treatment for overdose is known; treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

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

Pharmacodynamic effects

The elimination of oestrogen-mediated growth stimulation is a prerequisite for tumour response in cases where the growth of tumour tissue depends on the presence of oestrogens and endocrine therapy is used. In post-menopausal women, oestrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens - primarily androstenedione and testosterone - to oestrone and oestradiol. The suppression of oestrogen biosynthesis in peripheral tissues and the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme.

Letrozole is a non-steroidal aromatase inhibitor. It inhibits the aromatase enzyme by competitively binding to the haem of the aromatase cytochrome P450, resulting in a reduction of oestrogen biosynthesis in all tissues where

present.

In healthy post-menopausal women, single doses of 0.1, 0.5, and 2.5 mg letrozole suppress serum oestrone and oestradiol by 75-78% and 78% from baseline respectively. Maximum suppression is achieved in 48-78 h.

In post-menopausal patients with advanced breast cancer, daily doses of 0.1 to 5 mg suppress plasma concentration of oestradiol, oestrone, and oestrone sulphate by 75-95% from baseline in all patients treated. With doses of 0.5 mg and higher, many values of oestrone and oestrone sulphate are below the limit of detection in the assays, indicating that higher oestrogen suppression is achieved with these doses. Oestrogen suppression was maintained throughout treatment in all these patients.

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

No changes were noted in plasma concentrations of androgens (androstenedione and testosterone) among healthy post-menopausal women after 0.1, 0.5, and 2.5 mg single doses of letrozole or in plasma concentrations of androstenedione among post-menopausal patients treated with daily doses of 0.1 to 5 mg, indicating that the blockade of oestrogen biosynthesis does not lead to accumulation of androgenic precursors. Plasma levels of LH and FSH are not affected by letrozole in patients, nor is thyroid function as evaluated by TSH, T4 and T3 uptake test.

Adjuvant treatment

A multicentre, double-blind study randomised over 8,000 post-menopausal women with resected receptor-positive early breast cancer, to one of the following options:

Option 1:
- A: tamoxifen for 5 years
- B: letrozole for 5 years
- C: tamoxifen for 2 years followed by letrozole for 3 years
- D: letrozole for 2 years followed by tamoxifen for 3 years

Option 2:
- A: tamoxifen for 5 years
- B: letrozole for 5 years

Data in Table 2 reflect results based on data from the monotherapy arms in

each randomisation option and data from the two switching arms up to 30 days after the date of switch. The analysis of monotherapy *vs.* sequencing of endocrine treatments will be conducted when the necessary number of events has been achieved.

Patients have been followed for a median of 26 months, 76% of the patients for more than 2 years, and 16% (1,252 patients) for 5 years or longer.

The primary endpoint of the trial was disease-free survival (DFS) which was assessed as the time from randomisation to the earliest event of loco-regional or distant recurrence (metastases) of the primary disease, development of invasive contralateral breast cancer, appearance of a second non-breast primary tumour or death from any cause without a prior cancer event. Letrozole reduced the risk of recurrence by 19% compared with tamoxifen (hazard ratio 0.81; *P*=0.003). The 5-year DFS rates were 84.0% for letrozole and 81.4% for tamoxifen. The improvement in DFS with letrozole is seen as early as 12 months and is maintained beyond 5 years. Letrozole also significantly reduced the risk of recurrence compared with tamoxifen whether prior adjuvant chemotherapy was given (hazard ratio 0.72; *P*=0.018) or not (hazard ratio 0.84 ; *P*=0.044).

For the secondary endpoint overall survival a total of 358 deaths were reported (166 on letrozole and 192 on tamoxifen). There was no significant difference between treatments in overall survival (hazard ratio 0.86; P=0.15). Distant disease-free survival (distant metastases), a surrogate for overall survival, differed significantly overall (hazard ratio 0.73; P=0.001) and in pre-specified stratification subsets. Letrozole significantly reduced the risk of systemic failure by 17% compared with tamoxifen (hazard ratio 0.83; P=0.02)

However, although in favour of letrozole, a non-significant difference was obtained in contralateral breast cancer (hazard ratio 0.61; *P*=0.09). An exploratory analysis of DFS by nodal status showed that letrozole was significantly superior to tamoxifen in reducing the risk of recurrence in patients with node-positive disease (HR 0.71; 95% CI 0.59, 0.85; *P*=0.0002) while no significant difference between treatments was apparent in patients with node-negative disease (HR 0.98; 95% CI 0.77, 1.25; *P*=0.89). This reduced benefit in node-negative patients was confirmed by an exploratory interaction analysis (*P*=0.03).

Patients receiving letrozole, compared to tamoxifen, had fewer second malignancies (1.9% *vs*. 2.4%). Particularly the incidence of endometrial cancer was lower with letrozole compared to tamoxifen (0.2% *vs.* 0.4%).

See Tables 2 and 3 that summarise the results. The analyses summarised in Table 4 omit the 2 sequential arms from randomisation option 1, *i.e.* take account only of the monotherapy arms:

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

	Letrozole n=4,003	**Tamoxifen n=4,007**	**Hazard ratio (95% CI)**	***P*-value[1]**
Disease-free survival (primary) - events (protocol definition, total)	351	428	0.81 (0.70, 0.93)	0.0030
Distant disease-free survival (metastases) (secondary)	184	249	0.73 (0.60, 0.88)	0.0012
Overall survival (secondary) - number of deaths (total)	166	192	0.86 (0.70, 1.06)	0.1546
Systemic disease-free survival (secondary)	323	383	0.83 (0.72, 0.97)	0.0172
Contralateral breast cancer (invasive) (secondary)	19	31	0.61 (0.35, 1.08)	0.0910

CI = confidence interval
[1] Logrank test, stratified by randomisation option and use of prior adjuvant chemotherapy

Table 3 Disease-free and overall survival by nodal status and prior adjuvant chemotherapy (ITT population)

	Hazard Ratio, 95% CI for hazard ratio	***P*-value[1]**
Disease-free survival		
Nodal status		
- Positive	0.71 (0.59, 0.85)	0.0002
- Negative	0.98 (0.77, 1.25)	0.8875
Prior adjuvant chemotherapy		
- Yes	0.72 (0.55, 0.95)	0.0178
- No	0.84 (0.71, 1.00)	0.0435
Overall survival		
Nodal status		
- Positive	0.81 (0.63, 1.05)	0.1127
- Negative	0.88 (0.59, 1.30)	0.5070
Prior adjuvant chemotherapy		
- Yes	0.76 (0.51, 1.14)	0.1848
- No	0.90 (0.71, 1.15)	0.3951
Distant disease-free survival		
Nodal status		
- Positive	0.67 (0.54, 0.84)	0.0005
- Negative	0.90 (0.60, 1.34)	0.5973
Prior adjuvant		

chemotherapy - Yes - No	 0.69 (0.50, 0.95) 0.75 (0.60, 0.95)	 0.0242 0.0184

CI = confidence interval
[1] Cox model significance level

Table 4 Primary core analysis: efficacy endpoints according to randomisation option monotherapy arms (ITT population)

Endpoint	Option	Statistic	Letrozole	Tamoxifen
DFS (primary, protocol definition)	1	Events / n	100 / 1,546	137 / 1,548
		HR (95% CI), *P*	0.73 (0.56, 0.94), 0.0159	
	2	Events / n	177 / 917	202 / 911
		HR (95% CI), *P*	0.85 (0.69, 1.04), 0.1128	
	Overall	Events / n	277 / 2,463	339 / 2,459
		HR (95% CI), *P*	0.80 (0.68, 0.94), 0.0061	
DFS (excluding second malignancies)	1	Events / n	80 / 1,546	110 / 1,548
		HR (95% CI), *P*	0.73 (0.54, 0.97), 0.0285	
	2	Events / n	159 / 917	187 / 911
		HR (95% CI), *P*	0.82 (0.67, 1.02), 0.0753	
	Overall	Events / n	239 / 2,463	297 / 2,459
		HR (95% CI), *P*	0.79 (0.66, 0.93), 0.0063	
Distant DFS (secondary)	1	Events / n	57 / 1,546	72 / 1,548
		HR (95% CI), *P*	0.79 (0.56, 1.12), 0.1913	
	2	Events / n	98 / 917	124 / 911
		HR (95% CI), *P*	0.77 (0.59, 1.00), 0.0532	
	Overall	Events / n	155 / 2,463	196 / 2,459
		HR (95% CI), *P*	0.78 (0.63, 0.96), 0.0195	
Overall survival (secondary)	1	Events / n	41 / 1,546	48 / 1,548
		HR (95% CI), *P*	0.86 (0.56, 1.30), 0.4617	
	2	Events / n	98 / 917	116 / 911
		HR (95% CI), *P*	0.84 (0.64, 1.10), 0.1907	
	Overall	Events / n	139 / 2,463	164 / 2,459
		HR (95% CI), *P*	0.84 (0.67, 1.06), 0.1340	

P-value given is based on log rank test, stratified by adjuvant chemotherapy for each randomisation option, and by randomisation option and adjuvant chemotherapy for overall analysis

The median duration of treatment (safety population) was 25 months, 73% of the patients were treated for more than 2 years, 22% of the patients for more than 4 years. The median duration of follow-up was 30 months for both letrozole and tamoxifen.

Adverse events suspected of being related to study treatment were reported for 78% of the patients treated with letrozole compared with 73% of those treated with tamoxifen. The most common adverse events experienced with letrozole were hot flushes, night sweats, arthralgia, weight increase, and nausea. Of these, only arthralgia occurred significantly more often with letrozole than with tamoxifen (20% *vs*. 13% for tamoxifen). Letrozole treatment was associated with a higher risk of osteoporosis (2.2% *vs*. 1.2% with tamoxifen).

Overall, irrespective of causality, cardiovascular/cerebrovascular events were reported any time after randomisation for similar proportions of patients in both treatment arms (10.8% for letrozole, 12.2% for tamoxifen). Amongst these, thromboembolic events were reported significantly less often with letrozole (1.5%) than with tamoxifen (3.2%) ($P<0.001$), while cardiac failure was reported significantly more often with letrozole (0.9%) than with tamoxifen (0.4%) ($P=0.006$). Amongst patients who had baseline values of total serum cholesterol within the normal range, increases in total serum cholesterol higher than 1.5 times the ULN were observed in 5.4% of the patients in the letrozole arm, compared with 1.1% in the tamoxifen arm.

Extended adjuvant treatment

In a multicentre, double-blind, randomised, placebo-controlled study, performed in over 5,100 post-menopausal patients with receptor-positive or unknown primary breast cancer, patients who had remained disease-free after completion of adjuvant treatment with tamoxifen (4.5 to 6 years) were randomly assigned either letrozole or placebo.

The primary analysis conducted at a median follow-up of around 28 months (25% of patients being followed for at least 38 months) showed that letrozole reduced the risk of recurrence by 42% compared with placebo (hazard ratio 0.58; $P=0.00003$). The statistically significant benefit in DFS in favour of letrozole was observed regardless of nodal status: node-negative hazard ratio 0.48; $P=0.002$; node-positive hazard ratio 0.61; $P=0.002$.

For the secondary endpoint, overall survival (OS), a total 113 deaths were reported (51 letrozole, 62 placebo). Overall, there was no significant difference between treatments in OS (hazard ratio 0.82; $P=0.29$).

Afterwards the study continued in an unblinded fashion and patients in the placebo arm could switch to letrozole if they wished to do so. After the study unblinding, over 60% of the patients in the placebo arm eligible to switch opted to switch to letrozole (*i.e.* late extended adjuvant population). Patients who switched to letrozole from placebo had been off adjuvant tamoxifen for a median of 31 months (range 14 to 79 months).

Updated intent-to-treat analyses were conducted at a median follow-up of 49 months. In the letrozole arm at least 30% of the patients had completed 5 years and 59% had completed at least 4 years of follow-up.

In the updated analysis of DFS, letrozole significantly reduced the risk of breast cancer recurrence compared with placebo (hazard ratio 0.68; 95% CI 0.55, 0.83; $P=0.0001$). Letrozole also significantly reduced the odds of a new invasive contralateral cancer by 41% compared with placebo (odds ratio 0.59; 95% CI 0.36, 0.96; $P=0.03$). There was no significant difference in distant disease-free survival or overall survival.

Updated results (median duration of follow-up was 40 months) from the bone mineral density (BMD) sub-study (226 patients enrolled) demonstrated that, at

2 years, compared to baseline, patients receiving letrozole were associated with greater decreases in BMD in the total hip (median decreases of 3.8% in hip BMD compared to a median decrease of 2.0% in the placebo group (*P*=0.012, adjusted for bisphosphonate use, *P*=0.018)). Patients receiving letrozole were associated with a greater decrease in lumbar spine BMD although not significantly different.

Concomitant calcium and vitamin D supplementation was mandatory in the BMD sub-study.

Updated results (median duration of follow-up was 50 months) from the lipid sub-study (347 patients enrolled) show no significant differences between the letrozole and placebo arms in total cholesterol or in any lipid fraction.

In the updated analysis of the core study 11.1% of patients in the letrozole arm reported cardiovascular adverse events during treatment compared with 8.6% in the placebo arm until switch. These events included myocardial infarction (letrozole 1.3%, placebo 0.9%); angina requiring surgical intervention (letrozole 1.0%, placebo 0.8%), new or worsening angina (letrozole 1.7%, palcebo 1.2%), thromboembolic events (letrozole 1.0%, placebo 0.6%) and cerebrovascular accident (letrozole 1.7%, placebo 1.3%).

No significant differences were observed on global physical and mental summary scores, suggesting that overall, letrozole did not worsen quality of life relative to placebo. Treatment differences in favour of placebo were observed in patients' assessments with particularly the measures of physical functioning, bodily pain, vitality, sexual and vasomotor items. Although statistically significant these differences were not considered clinically relevant.

First-line treatment

One controlled double-blind trial was conducted comparing letrozole 2.5 mg to tamoxifen 20 mg as first-line therapy in post-menopausal women with advanced breast cancer. In 907 women, letrozole was superior to tamoxifen in time to progression (primary endpoint) and in overall objective response, time to treatment failure and clinical benefit.

The results are summarised in Table 5:

Table 5 Results at a median follow-up of 32 months

Variable	**Statistic**	**Letrozole n=453**	**Tamoxifen n=454**
Time to progression	Median	9.4 months	6.0 months
	(95% CI for median)	(8.9, 11.6 months)	(5.4, 6.3 months)
	Hazard ratio (HR)	0.72	
	(95% CI for HR)	(0.62, 0.83)	
	P	<0.0001	
Objective response rate	CR+PR	145 (32%)	95 (21%)

(ORR)	(95% CI for rate)	(28, 36%)	(17, 25%)
	Odds ratio	1.78	
	(95% CI for odds ratio)	(1.32, 2.40)	
	P	0.0002	
Overall clinical benefit rate	CR+PR+NC≥24 weeks	226 (50%)	173 (38%)
	Odds ratio	1.62	
	(95% CI for odds ratio)	(1.24, 2.11)	
	P	0.0004	
Time to treatment failure	Median	9.1 months	5.7 months
	(95% CI for median)	(8.6, 9.7 months)	(3.7, 6.1 months)
	Hazard ratio	0.73	
	(95% CI for HR)	(0.64, 0.84)	
	P	<0.0001	

Time to progression was significantly longer, and response rate was significantly higher for letrozole than for tamoxifen in patients with tumours of unknown receptor status as well as with positive receptor status. Similarly, time to progression was significantly longer, and response rate significantly higher for letrozole irrespective of whether adjuvant anti-oestrogen therapy had been given or not. Time to progression was significantly longer for letrozole irrespective of dominant site of disease. Median time to progression was almost twice as long for letrozole in patients with soft tissue disease only (median 12.1 months for letrozole, 6.4 months for tamoxifen), and in patients with visceral metastases (median 8.3 months for letrozole, 4.6 months for tamoxifen). Response rate was significantly higher for letrozole in patients with soft tissue disease only (50% *vs*. 34% for letrozole and tamoxifen respectively), and for patients with visceral metastases (28% letrozole *vs*. 17% tamoxifen).

Study design allowed patients to cross over upon progression to the other therapy or discontinue from the study. Approximately 50% of patients crossed over to the opposite treatment arm and cross-over was virtually completed by 36 months. The median time to cross-over was 17 months (letrozole to tamoxifen) and 13 months (tamoxifen to letrozole).

Letrozole treatment in the first-line therapy of advanced breast cancer resulted in a median overall survival of 34 months compared with 30 months for tamoxifen (log rank test *P*=0.53, not significant). Better survival was associated with letrozole up to at least 24 months. The survival rate at 24 months was 64% for the letrozole treatment group *vs.* 58% for the tamoxifen group. The absence of an advantage for letrozole on overall survival could be explained by the cross-over design of the study.

The total duration of endocrine therapy ('time to chemotherapy') was significantly longer for letrozole (median 16.3 months, 95% CI 15 to 18 months) than for tamoxifen (median 9.3 months, 95% CI 8 to 12 months) (log rank *P*=0.0047).

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 post-menopausal women with advanced breast cancer previously treated with anti-oestrogens.

Time to progression was not significantly different between letrozole 2.5 mg and megestrol acetate (*P*=0.07). Statistically significant differences were observed in favour of letrozole 2.5 mg compared to megestrol acetate in overall objective tumour response rate (24% *vs* 16%, *P*=0.04), and in time to treatment failure (*P*=0.04). Overall survival was not significantly different between the 2 arms (*P*=0.2).

In the second study, the response rate was not significantly different between letrozole 2.5 mg and aminoglutethimide (*P*=0.06). Letrozole 2.5 mg was statistically superior to aminoglutethimide for time to progression (*P*=0.008), time to treatment failure (*P*=0.003) and overall survival (*P*=0.002).

5.2 Pharmacokinetic properties

Absorption

Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability: 99.9%). Food slightly decreases the rate of absorption (median t_{max} 1 hour fasted *vs.* 2 hours fed; and mean C_{max} 129 ± 20.3 nmol/L fasted *vs.* 98.7 ± 18.6 nmol/L fed) but the extent of absorption (AUC) is not changed. The minor effect on the absorption rate is not considered to be of clinical relevance, and therefore letrozole may be taken without regard to mealtimes.

Distribution

Plasma protein binding of letrozole is approximately 60%, mainly to albumin (55%). The concentration of letrozole in erythrocytes is about 80% of that in plasma. After administration of 2.5 mg ^{14}C-labelled letrozole, approximately 82% of the radioactivity in plasma was unchanged compound. Systemic exposure to metabolites is therefore low. Letrozole is rapidly and extensively distributed to tissues. Its apparent volume of distribution at steady state is about 1.87 ± 0.47 L/kg.

Metabolism and elimination

Metabolic clearance to a pharmacologically inactive carbinol metabolite is the major elimination pathway of letrozole (CL_m= 2.1 L/h) but is relatively slow when compared to hepatic blood flow (about 90 L/h). The cytochrome P450 isoenzymes 3A4 and 2A6 were found to be capable of converting letrozole to this metabolite.

Formation of minor unidentified metabolites and direct renal and faecal excretion play only a minor role in the overall elimination of letrozole. Within

2 weeks after administration of 2.5 mg ^{14}C-labelled letrozole to healthy post-menopausal volunteers, 88.2 ± 7.6% of the radioactivity was recovered in urine and 3.8 ± 0.9% in faeces. At least 75% of the radioactivity recovered in urine up to 216 hours (84.7 ± 7.8% of the dose) was attributed to the glucuronide of the carbinol metabolite, about 9% to two unidentified metabolites, and 6% to unchanged letrozole.

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

Age had no effect on the pharmacokinetics of letrozole.

Special populations

In a study involving 19 volunteers with varying degrees of renal function (24-hour creatinine clearance 9-116 mL/min) no effect on the pharmacokinetics of letrozole was found after a single dose of 2.5 mg. In a similar study involving subjects with varying degrees of hepatic function, the mean AUC values of the volunteers with moderate hepatic impairment (Child-Pugh score B) was 37% higher than in normal subjects, but still within the range seen in subjects without impaired function. In a study comparing the pharmacokinetics of letrozole after a single oral dose in eight male subjects with liver cirrhosis and severe hepatic impairment (Child-Pugh score C) to those in healthy volunteers (n=8), AUC and $t_{½}$ increased by 95 and 187%, respectively. Thus letrozole should be administered with caution and after consideration of the potential risk/benefit to such patients.

5.3 Preclinical safety data

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

Letrozole showed a low degree of acute toxicity in rodents exposed up to 2,000 mg/kg. In dogs it caused signs of moderate toxicity at 100 mg/kg.

In repeated-dose toxicity studies in rats and dogs up to 12 months, the main findings observed can be attributed to the pharmacological action of the compound. The no-adverse-effect level was 0.3 mg/kg in both species.

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

In a 104-week rat carcinogenicity study, no treatment-related tumours were noted in male rats. In female rats, a reduced incidence of benign and malignant

mammary tumours at all the doses of letrozole was found.

Oral administration of letrozole to gravid rats resulted in a slight increase in the incidence of fetal malformation among the animals treated. However, it was not possible to show whether this was an indirect consequence of the pharmacological properties (inhibition of oestrogen biosynthesis) or a direct effect of letrozole in its own right (see recommendation in sections 4.3, and 4.6).

Preclinical observations were confined to those associated with the recognised pharmacological action, which is the only safety concern for human use derived from animal studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Cellulose, microcrystalline
Starch (maize)
Magnesium stearate
Lactose, monohydrate
Silica, colloidal anhydrous
Sodium starch glycollate (type A)

Film-coating:
Opadry II 85F32723 Yellow consisting of:
Iron oxide, yellow (E172)
Macrogol 3350
Titanium dioxide (E171)
Talc
Indigo carmine aluminium lake (E132)
Poly(vinyl alcohol)
Tartrazine aluminium lake (E102)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Transparent PVC/PVdC-aluminium blisters.

Pack sizes: 1, 10, 14, 15, 20, 28, 30, 60, 90, 98 and 100 film-coated tablets; hospital pack of 50 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER

TEVA UK Limited
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex,
BN22 9AG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/1168

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/01/2010

10 DATE OF REVISION OF THE TEXT

14/01/2010

Module 3

Product Information Leaflet

LETROZOLE 2.5 mg FILM-COATED TABLETS

PACKAGE LEAFLET: INFORMATION FOR THE USER

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

IN THIS LEAFLET:

1 WHAT LETROZOLE 2.5 mg FILM-COATED TABLETS IS AND WHAT IT IS USED FOR

What Letrozole is
Letrozole contains an active substance called letrozole. It belongs to a group of medicines called aromatase inhibitors. It is a hormonal (or "endocrine") breast cancer treatment.

What Letrozole is used for
Letrozole is used to prevent breast cancer happening again. It can be used as a first treatment after breast surgery, or following five years of treatment with tamoxifen. Letrozole is also used to prevent breast tumour spreading to other parts of the body in patients with advanced breast cancer.
Letrozole should only be used for oestrogen receptor positive breast cancer and only in women after menopause i.e. cessation of periods.

How Letrozole works
Growth of breast cancer is frequently stimulated by oestrogens, which are female sex hormones. Letrozole reduces the amount of oestrogen by blocking an enzyme ("aromatase") involved in the production of oestrogens. As a consequence, tumour cells slow or stop the growing and/or spreading to other parts of the body.

Monitoring your Letrozole treatment
You should only take this medicine under strict medical supervision. Your doctor will regularly monitor your condition to check if the treatment is having the right effect. Letrozole may cause thinning or wasting of your bones (osteoporosis) due to the reduction of oestrogens in your body. This means that your doctor may decide to measure your bone density (a way of monitoring for osteoporosis) before, during and after treatment.

If you have any questions about how Letrozole works or why this medicine has been prescribed for you, ask your doctor.

2 BEFORE YOU TAKE LETROZOLE 2.5 mg FILM-COATED TABLETS

Follow all the doctor's instructions carefully. They may differ from the general information in this leaflet.

Do NOT take Letrozole if you:
- are allergic (hypersensitive) to letrozole or any of the other ingredients of this medicine listed in section 6 of this leaflet
- still have periods, i.e. if you have not yet gone through the menopause
- are pregnant
- are breast-feeding.

If any of these conditions apply to you, **do not take this medicine and talk to your doctor.**

Take special care with Letrozole if you have:
- a severe kidney disease
- a severe liver disease
- a history of osteoperosis or bone fractures (see also section 1 "Monitoring your Letrozole treatment").

If any of these conditions apply to you, **tell your doctor.** Your doctor will take this into account during your treatment with Letrozole.

Children and adolescents (below 18 years)
Children or adolescents should not use this medicine.

Older people (age 65 years and over)
People aged 65 years and over can use this medicine at the same dose as for other adults.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
You must not take Letrozole if you are pregnant or breast-feeding as it may harm your baby. Since Letrozole is only recommended for post-menopausal women, pregnancy and breast-feeding restrictions most likely will not apply to you. However, if you recently became post-menopausal or if you are peri-menopausal (pre-menopausal stage during which hormone levels are changing), your doctor should discuss with you about the necessity of a pregnancy test before taking Letrozole and of contraception as you might have the potential to become pregnant.

Driving and using machines
If you feel dizzy, tired, drowsy or generally unwell, do not drive or operate any tools or machines until you feel normal again.

Important information about some of the ingredients of Letrozole
This medicinal product contains **lactose**. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine. This medicinal product contains tartrazine aluminium lake (E102) and may cause allergic reactions.

3 HOW TO TAKE LETROZOLE 2.5 mg FILM-COATED TABLETS

Always take Letrozole exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

How much Letrozole to take
The usual dose is one tablet of Letrozole to be taken once a day. Taking Letrozole at the same time each day will help you remember when to take your tablet.

How to take Letrozole
The tablet should be swallowed whole with a glass of water or another liquid.

How long to take Letrozole
Continue taking Letrozole every day for as long as your doctor tells you. You may need to take it for months or even years. If you have any questions about how long to keep taking Letrozole, talk to your doctor.

If you take more Letrozole than you should
If you have taken too much Letrozole, or if someone else accidentally takes your tablets, contact your doctor or hospital for advice immediately. Show them the pack of tablets. Medical treatment may be necessary.

If you forget to take Letrozole
- if it is almost time for your next dose (e.g. within 2 or

3 hours), skip the dose you missed and take your next dose when you are meant to.
- otherwise, take the dose as soon as you remember, and then take the next tablet as you would normally.
- do not take a double dose to make up for the one that you missed.

If you stop taking Letrozole
Do not stop taking Letrozole unless your doctor tells you. See also the section above, "How long to take Letrozole". If you have any further questions on the use of this product, ask your doctor or pharmacist.

4 POSSIBLE SIDE EFFECTS

Like all medicines, Letrozole can cause side effects, although not everybody gets them. Most of the side effects are mild to moderate and will generally disappear after a few days to a few weeks of treatment. Some of these side effects, such as hot flushes, hair loss or vaginal bleeding, may be due to the lack of oestrogens in your body. Do not be alarmed by this list of possible side effects. You may not experience any of them.

Some side effects could be serious:
Rare or uncommon (i.e. they may affect 1 to 100 users in 10,000):
- if you experience weakness, paralysis or loss of feeling in an arm or leg or any other part of the body, loss of coordination, nausea, or difficulty in speaking or breathing (sign of a brain disorder, e.g. stroke)
- if you have sudden oppressive chest pain (sign of a heart disorder)
- if you experience difficulty in breathing, chest pain, fainting, rapid heart rate, bluish skin discolouration, or sudden arm or leg (foot) pain (signs that a blood clot may have formed)
- if you experience swelling and redness along a vein which is extremely tender and possibly painful when touched
- if you get severe fever, chills or mouth ulcers due to infections (lack of white blood cells)
- if you get severe persistent blurred vision.

Some patients experienced other side effects during treatment with Letrozole:
- swelling mainly of the face and throat (signs of an allergic reaction)
- yellow skin and eyes, nausea, loss of appetite, dark coloured urine (signs of hepatitis)
- rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever (signs of skin disorder).

If any of the above occur, tell your doctor straight away.
Some side effects are very common. These side effects may affect more than 1 user in 10 patients.
- hot flushes
- fatigue
- increased sweating
- pain in bones and joints (arthralgia).

If any of these affects you severely, tell your doctor.
Some side effects are common. These side effects may affect 1 to 10 users in 100.
- skin rash
- headache
- dizziness
- malaise (generally feeling unwell)
- gastrointestinal disorders such as nausea, vomiting, indigestion, constipation, diarrhoea
- increase in or loss of appetite
- pain in muscles
- thinning or wasting of your bones (osteoporosis), leading to bone fractures in some cases (see also section 1, "Monitoring your Letrozole treatment")
- swelling of arms, hands, feet, ankles (oedema)
- sad mood (depression)
- weight increase
- hair loss.

If any of these affects you severely, tell your doctor.
Other side effects are uncommon. These side effects may affect 1 to 10 users in 1,000.
- nervous disorders such as anxiety, nervousness, irritability, drowsiness, memory problems, somnolence, insomnia
- impairment of sensation, especially that of touch
- eye disorders such as blurred vision, eye irritation
- palpitations, rapid heart rate, raised blood pressure (hypertension)
- skin disorders such as itching (urticaria), dry skin
- vaginal disorders such as bleeding, discharge or dryness
- abdominal pain
- joint stiffness (arthritis)
- breast pain
- fever
- thirst, taste disorder, dry mouth
- dryness of mucous membranes
- weight decrease
- urinary tract infection, increased frequency of urination
- cough.

If any of these affects you severely, tell your doctor.
You may also have some blood test disorders while taking Letrozole, i.e. high levels of cholesterol (hypercholesterolaemia) or high levels of liver enzymes.
If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5 HOW TO STORE LETROZOLE 2.5 mg FILM-COATED TABLETS

- **Keep out of the reach and sight of children.**
- Do not use Letrozole after the expiry date which is stated on the blister and carton after 'EXP'. The expiry date refers to the last day of that month.
- This medicinal product does not require any special storage conditions.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 FURTHER INFORMATION

What Letrozole 2.5 mg Film-Coated Tablets contain
- The active ingredient is letrozole. Each film-coated tablet contains 2.5 mg letrozole.
- The other ingredients are cellulose microcrystalline, starch (maize), magnesium stearate, lactose monohydrate, silica colloidal anhydrous, sodium starch glycolate (type A) and Opadry II 85F32723 Yellow which consists of iron oxide yellow (E172), macrogol 3350, titanium dioxide (E171), talc, indigo carmine aluminium lake (E132), poly(vinyl alcohol) and tartrazine aluminium lake (E102).

What Letrozole 2.5 mg Film-Coated Tablets look like and contents of the pack
- Letrozole 2.5 mg Film-Coated Tablets are dark yellow, standard convex round, film-coated tablets debossed with "93" on one side and "B1" on the other side.
- Letrozole 2.5 mg Film-Coated Tablets are available in pack sizes of 1, 10, 14, 15, 20, 28, 30, 60, 90, 98 and 100 film-coated tablets; hospital pack of 50 film-coated tablets are also available. Not all pack sizes may be marketed.

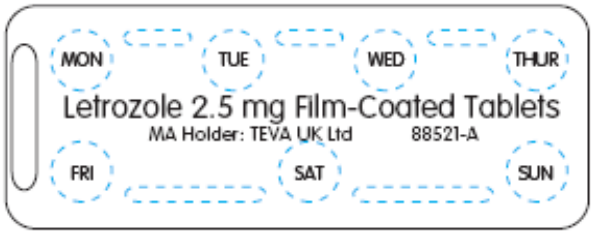
Marketing Authorisation Holder and Manufacturer
TEVA UK Limited, Eastbourne, BN22 9AG.

This leaflet was last revised in December 2009.
88522-A

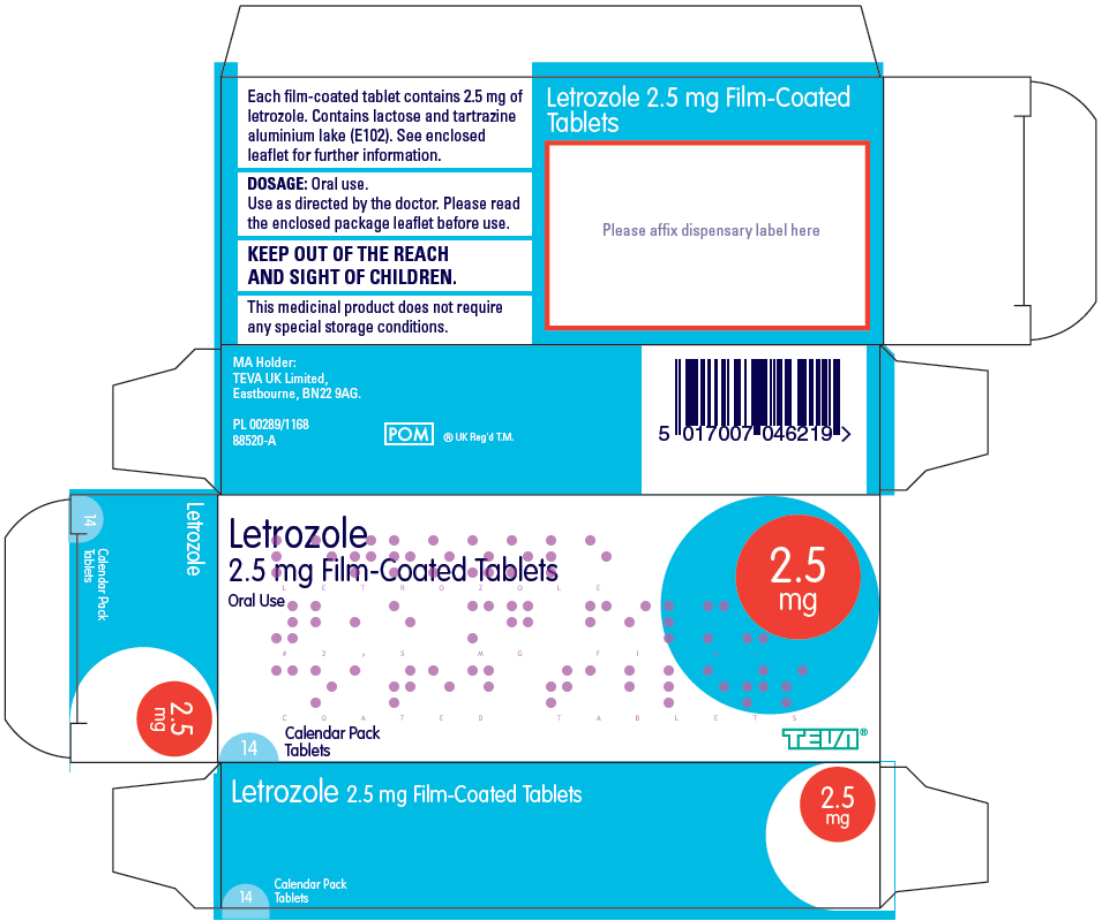
Module 4

Labelling

Blister:



Carton:


Each film-coated tablet contains 2.5 mg of letrozole. Contains lactose and tartrazine aluminium lake (E102). See enclosed leaflet for further information.
DOSAGE: Oral use.
Use as directed by the doctor. Please read the enclosed package leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
This medicinal product does not require any special storage conditions.
Letrozole 2.5 mg Film-Coated Tablets
Please affix dispensary label here
MA Holder:
TEVA UK Limited,
Eastbourne, BN22 9AG.
PL 00289/1168
88520-A
POM
® UK Reg'd T.M.
5 017007 046219
Letrozole
14 Calendar Pack Tablets
2.5 mg
Letrozole
2.5 mg Film-Coated Tablets
Oral Use
2.5 mg
14 Calendar Pack Tablets
TEVA
Letrozole 2.5 mg Film-Coated Tablets
2.5 mg
14 Calendar Pack Tablets

Module 5

Scientific discussion during initial procedure

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Letrozole 2.5 mg Film-coated Tablets, in the treatment of breast cancer, is approvable.

EXECUTIVE SUMMARY

Problem statement
This decentralised application concerns a generic version of letrozole, submitted under Article 10.1.

The UK reference product Femara® 2.5 mg Tablets (Novartis Pharmaceuticals UK Ltd) was first registered on 18 November 1996. The original product is listed as Femara 2.5 mg comprime pellicule and was licensed on 24 July 1996 in France.

With the UK as the Reference Member State in this Decentralised Procedure, TEVA UK Limited is applying for a marketing authorisation for Letrozole 2.5 mg Film-coated Tablets in AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, NL, NO, PL, PT, RO, SE and SI.

About the product
The active substance, letrozole, is a reversible (type II), nonsteroidal aromatase inhibitor. The aromatase enzyme is involved in the production of oestrogen. In postmenopausal women the aromatase enzyme converts the sex hormones androstenedione and testosterone into oestrogen. Letrozole prevents this conversion by blocking the action of the aromatase enzyme, thus causing oestrogen levels in the body to fall. The majority of patients with breast cancer have oestrogen dependent, hormone receptor positive disease. Reducing the levels of circulating oestrogen is a well established treatment in the management of breast cancer.

The proposed indication is:

"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 post-menopausal status after relapse or disease progression, who have previously been treated with anti-oestrogens.

Efficacy has not been demonstrated in patients with hormone receptor-negative breast cancer."

The proposed posology is:

"Adults 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 (see sections 4.4 and 5.2)."

As the proposed posolgy and indications are in line with the reference product, they are satisfactory.

General comments on the submitted dossier
The dossier is considered adequate.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The submitted clinical bioequivalence study was conducted in line with GCP.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substance
The chemical-pharmaceutical documentation and Expert Report in relation to Letrozole 2.5 mg Film-coated Tablets are of sufficient quality in view of the present European regulatory requirements. The drug substance specification for the drug substance is acceptable. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed and the results support the proposed re-test period

Drug Product
The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis results show that the finished products meet the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. The stability data support the proposed shelf-life of 30 months with no special storage precautions.

Non clinical aspects
The pharmacological, pharmacokinetic and toxicological properties of letrozole are well known. As letrozole is a well known active substance, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

The non-clinical overview has been written by a pharmacist. The overview, dated May 2008, refers to five references from the published literature dated 1993 to 2008. Although the overview is very brief, the expert has specifically stated that a literature search revealed no new animal results likely to influence the known safety profile of letrozole. Therefore, the overview is acceptable in view of the fact that the toxicological properties of letrozole are well known.

There are no objections to the approval of Letrozole 2.5mg Film-coated Tablets from a non-clinical point of view.

Clinical aspects

Pharmacokinetics
The applicant has submitted a bioequivalence study comparing the bioavailability between letrozole 2.5 mg tablets and the reference product Femara® 2.5 mg Tablets (UK market) in healthy subjects.

This was an open-label, randomised, two-treatment, two period, two-sequence, single dose of 1 x 2.5 mg tablet, crossover study, undertaken in adult, healthy female subjects under fasting conditions .

Sampling schedule during each period included samples taken at pre-dose and at fixed intervals post dose. There was a 28 day washout period.
Healthy adult post-menopausal or surgically sterile female volunteers were enrolled in the study:

- 28 subjects were dosed in period 1
- 27 subjects were dosed in period 2
- 26 subjects were included in the PK analysis

One subject) was excluded from the PK analysis since the pre-dose plasma level of letrozole in period 2 was greater than 5% of Cmax for that period. This was in line with study protocol. Another subject was withdrawn after dosing period 1 due to failure to return for blood collections.

Test: Letrozole 2.5 mg film-coated tablets (Teva)
Reference: Femara® 2.5 mg Tablets (Novartis Pharmaceuticals UK Ltd)

Plasma concentrations of letrozole were determined using a validated LC-MS/MS method

The pharmacokinetic parameters for this study were C_{max} and AUC as well as T_{max}, K_{el} and $t_{½}$ ANOVA was carried out for un-transformed $t_{½}$ and K_{el} and log-transformed AUC and C_{max} parameters. Criteria for bioequivalence consisted of 90% CI of the relative mean AUC and Cmax of the test to the reference should fall between 80-125%.

Results

Analyte: Letrozole (N = 26)

Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
	Treatment A	Treatment B			
AUCt (ng·h/mL)	1675.006 1739.524 (28)	1660.853 1716.874 (26)	100.85	98.34 - 103.43	5
AUCinf (ng·h/mL)	1786.100 1879.334 (33)	1778.796 1858.185 (31)	100.41	97.63 - 103.27	6
Cmax (ng/mL)	40.107 40.869 (20)	39.431 40.819 (26)	101.71	95.15 - 108.73	14
Tmax[a] (h)	1.39 (55)	1.49 (64)	-	-	-
Kel[a] (1/h)	0.0135 (32)	0.0131 (31)	-	-	-
Thalf[a] (h)	56.88 (35)	58.04 (33)	-	-	-

[a]Presented as arithmetic mean (CV%).

There were no significant adverse events reported in the study and both formulations were well tolerated.

Conclusion:

Based on the submitted bioequivalence study Letrozole 2.5mg film coated tablets are considered bioequivalent to Femara® 2.5 mg Tablets as the 90% confidence intervals for AUC_{0-t} and C_{max} fall within the 80 to 125% confidence limits set out in the Note for Guidance on the Investigation of Bioavailability (CPMP/EWP/QWP/1401/98).

Pharmacodynamics
No new data have been submitted and none are required.

Clinical efficacy
No new efficacy data have been submitted and none are required for this application.

Clinical safety
No new safety data have been submitted and none are required for this application.

Pharmacovigilance system
The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan
No description of RMP has been provided. As this application concerns a generic with a reference product for which no safety concern requiring risk minimisation activities have been identified this approach is acceptable.

Periodic Safety Update Report (PSUR)
The PSUR submission schedule proposed for this product is satisfactory as it contains a known active substance which has been marketed for many years throughout the EU.

BENEFIT RISK ASSESSMENT
The benefit-risk ratio is considered favourable. Approval of a Marketing Authorisation is recommended.