Public Assessment Report

Decentralised Procedure

LETROZOLE 2.5MG FILM-COATED TABLETS

Procedure No: UK/H/1367/001/DC

UK Licence No: PL 10622/0339

PLIVA PHARMA LIMITED
LAY SUMMARY

The MHRA granted PLIVA Pharma Limited Marketing Authorisations (licences) for the medicinal product Letrozole 2.5mg Film-Coated Tablets on 16th June 2009. This prescription-only medicine is used to treat oestrogen receptor-positive breast cancer in post-menopausal women i.e. after the cessation of periods has occurred. Letrozole is used to prevent breast cancer happening again.

Letrozole belongs to a group of medicines called aromatase inhibitors. It is a hormonal (or “endocrine”) breast cancer treatment.

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.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Letrozole 2.5mg Film-Coated Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
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</table>
## Module 1

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Letrozole 2.5mg Film-Coated Tablets</th>
</tr>
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<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td>Active Substance</td>
<td>Letrozole</td>
</tr>
<tr>
<td>Form</td>
<td>Film-Coated Tablets</td>
</tr>
<tr>
<td>Strength</td>
<td>2.5mg</td>
</tr>
<tr>
<td>MA Holder</td>
<td>PLIVA Pharma Limited Vision House, Bedford Road, Petersfield, Hampshire, GU32 3QB</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>UK</td>
</tr>
<tr>
<td>CMS</td>
<td>Bulgaria, the Czech Republic, Germany, Hungary, Ireland, Poland, Romania, Spain, Slovenia and the Slovak Republic</td>
</tr>
<tr>
<td>Procedure Number</td>
<td>UK/H/1367/001/DC</td>
</tr>
<tr>
<td>Timetable</td>
<td>Day 210 – 15th April 2009</td>
</tr>
</tbody>
</table>
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
Excipient(s):
Each tablet contains 64 mg of lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Ochre, round, biconvex film-coated tablets with ‘LT’ imprinted on one side and ‘2’ on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
• Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.
• Extended adjuvant treatment of hormone-dependent early breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy for 5 years.
• First-line treatment in postmenopausal 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. Efficacy has not been demonstrated in patients with hormone receptor negative breast cancer.

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 and Adolescents
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.
Premenopausal endocrine status; pregnancy; lactation (see sections 4.6 Pregnancy and lactation and 5.3 Preclinical safety data).

4.4 Special warnings and precautions for use
In patients whose postmenopausal 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 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 (see section 4.8).

Excipient warning
This medicinal product contains lactose, therefore 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 drugs does not result in clinically significant drug interactions. Additionally, a review of the clinical trial database indicated no evidence of clinically relevant interactions with other commonly prescribed drugs. There is no clinical experience to date on the use of letrozole in combination with other anticancer agents.

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

4.6 Pregnancy and lactation
Women of perimenopausal 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 perimenopausal or who recently became postmenopausal) until their postmenopausal 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 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 – 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 randomization 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 ≥ 10%, common ≥1% to < 10%, uncommon ≥ 0.1% to < 1%, rare ≥ 0.01% to < 0.1%, very rare <0.01%, including isolated reports.

<table>
<thead>
<tr>
<th>Infections and infestations</th>
<th>Uncommon: Urinary tract infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasms, benign, malignant and unspecified (including cysts and polyps)</td>
<td>Uncommon: Tumour pain (not applicable in the adjuvant and extended adjuvant setting)</td>
</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Uncommon: Leukopenia</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common: Anorexia, appetite increase, hypercholesterolaemia</td>
</tr>
<tr>
<td>Uncommon: General oedema</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common: Depression</td>
</tr>
<tr>
<td>Uncommon: Anxiety including nervousness, irritability</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common: Headache, dizziness</td>
</tr>
<tr>
<td>Uncommon: Somnolence, insomnia, memory impairment, dysesthesia including paresthesia, hypoesthesia, taste disturbance, cerebrovascular accident</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Uncommon Cataract, eye irritation, blurred vision</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon: Palpitations, tachycardia</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Uncommon: Thrombophlebitis including superficial and deep thrombophlebitis, hypertension, ischemic cardiac events</td>
</tr>
<tr>
<td>Rare: Pulmonary embolism, arterial thrombosis, cerebrovascular infarction</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Uncommon: Dyspnoea, cough</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common: Nausea, vomiting, dyspepsia, constipation, diarrhoea</td>
</tr>
<tr>
<td>Uncommon: Abdominal pain, stomatitis, dry mouth</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Uncommon: Increased hepatic enzymes</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Very common: Increased sweating</td>
</tr>
<tr>
<td>Common: Alopecia, rash including erythematous, maculopapular, psoriaform, and vesicular rash</td>
<td></td>
</tr>
<tr>
<td>Uncommon: Pruritus, dry skin, urticaria</td>
<td></td>
</tr>
<tr>
<td>Not known: Angioedema, anaphylactic reaction</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Very common: Arthralgia</td>
</tr>
<tr>
<td>Common: Myalgia, bone pain, osteoporosis, bone fractures</td>
<td></td>
</tr>
<tr>
<td>Uncommon: Arthritis</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Uncommon: Increased urinary frequency</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Uncommon: Vaginal bleeding, vaginal discharge, vaginal dryness, breast pain</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very common: Hot flushes, fatigue including asthenia</td>
</tr>
<tr>
<td>Common: Malaise, peripheral oedema</td>
<td></td>
</tr>
<tr>
<td>Uncommon: Pyrexia, mucosal dryness, thirst</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Common: Weight increase</td>
</tr>
<tr>
<td>Uncommon: Weight loss</td>
<td></td>
</tr>
</tbody>
</table>

4.9 Overdose
Isolated cases of overdosage with letrozole have been reported.
No specific treatment for overdosage is known; treatment should be symptomatic and supportive.
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 postmenopausal women, oestrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens - primarily androstenedione and testosterone - to oestrone (E1) and oestradiol (E2). 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 postmenopausal 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 postmenopausal 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-deoxycorticisol, 17-hydroxyprogesterone, and ACTH or in plasma renin activity among postmenopausal patients treated with a daily dose of letrozole 0.1 to 5 mg. The ACTH stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0.1, 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 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 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 multicenter, double-blind study randomized over 8000 postmenopausal women with resected receptor-positive early breast cancer, to one of the following option:
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 randomization 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% (1252 patients) for 5 years or longer.
The primary endpoint of the trial was disease-free survival (DFS) which was assessed as the time from randomization 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 non significant difference was obtained in the contralateral breast cancer (hazard ratio 0.61; P=0.09). An exploratory analysis of DFS by nodule 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 summarize the results. The analyses summarized in Table 4 omit the 2 sequential arms from randomization option 1, i.e. take account only of the monotherapy arms:

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

<table>
<thead>
<tr>
<th></th>
<th>Letrozole N=4003</th>
<th>Tamoxifen N=4007</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-Value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free survival (primary)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- events (protocol definition, total)</td>
<td>351</td>
<td>428</td>
<td>0.81 (0.70, 0.93)</td>
<td>0.0030</td>
</tr>
<tr>
<td>Distant disease-free survival (metastases) (secondary)</td>
<td>184</td>
<td>249</td>
<td>0.73 (0.60, 0.88)</td>
<td>0.0012</td>
</tr>
<tr>
<td>Overall survival (secondary)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- number of deaths (total)</td>
<td>166</td>
<td>192</td>
<td>0.86 (0.70, 1.06)</td>
<td>0.1546</td>
</tr>
<tr>
<td>Systemic disease-free survival (secondary)</td>
<td>323</td>
<td>383</td>
<td>0.83 (0.72, 0.97)</td>
<td>0.0172</td>
</tr>
<tr>
<td>Contralateral breast cancer (invasive) (secondary)</td>
<td>19</td>
<td>31</td>
<td>0.61 (0.35, 1.08)</td>
<td>0.0910</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio, 95% CI for hazard ratio</th>
<th>P-Value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0.71 (0.59, 0.85)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Negative</td>
<td>0.98 (0.77, 1.25)</td>
<td>0.8875</td>
</tr>
<tr>
<td>Prior adjuvant chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.72 (0.55, 0.95)</td>
<td>0.0178</td>
</tr>
<tr>
<td>No</td>
<td>0.84 (0.71, 1.00)</td>
<td>0.0435</td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0.81 (0.63, 1.05)</td>
<td>0.1127</td>
</tr>
<tr>
<td>Negative</td>
<td>0.88 (0.59, 1.30)</td>
<td>0.5070</td>
</tr>
</tbody>
</table>
Table 4: Primary Core Analysis: Efficacy endpoints according to randomization option

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Option</th>
<th>Statistic</th>
<th>Letrozole</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS (Primary, protocol definition)</td>
<td>1</td>
<td>Events / n</td>
<td>100 / 1546</td>
<td>137 / 1548</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR (95% CI), P</td>
<td>0.73 (0.56, 0.94), 0.0159</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Events / n</td>
<td>177 / 917</td>
<td>202 / 911</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR (95% CI), P</td>
<td>0.85 (0.69, 1.04), 0.1128</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>Events / n</td>
<td>277 / 2463</td>
<td>339 / 2459</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR (95% CI), P</td>
<td>0.80 (0.68, 0.94), 0.0061</td>
<td></td>
</tr>
<tr>
<td>DFS (excluding second malignancies)</td>
<td>1</td>
<td>Events / n</td>
<td>80 / 1546</td>
<td>110 / 1548</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Events / n</td>
<td>159 / 917</td>
<td>187 / 911</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR (95% CI), P</td>
<td>0.82 (0.67, 1.02), 0.0753</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>Events / n</td>
<td>239 / 2463</td>
<td>297 / 2459</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR (95% CI), P</td>
<td>0.79 (0.66, 0.93), 0.0063</td>
<td></td>
</tr>
<tr>
<td>Distant DFS (Secondary)</td>
<td>1</td>
<td>Events / n</td>
<td>57 / 1546</td>
<td>72 / 1548</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR (95% CI), P</td>
<td>0.79 (0.56, 1.12), 0.1913</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Events / n</td>
<td>98 / 917</td>
<td>124 / 911</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR (95% CI), P</td>
<td>0.77 (0.59, 1.00), 0.0532</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>Events / n</td>
<td>155 / 2463</td>
<td>196 / 2459</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR (95% CI), P</td>
<td>0.78 (0.63, 0.96), 0.0195</td>
<td></td>
</tr>
<tr>
<td>Overall survival (Secondary)</td>
<td>1</td>
<td>Events / n</td>
<td>41 / 1546</td>
<td>48 / 1548</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR (95% CI), P</td>
<td>0.86 (0.56, 1.30), 0.4617</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Events / n</td>
<td>98 / 917</td>
<td>116 / 911</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR (95% CI), P</td>
<td>0.84 (0.64, 1.10), 0.1907</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>Events / n</td>
<td>139 / 2463</td>
<td>164 / 2459</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR (95% CI), P</td>
<td>0.84 (0.67, 1.06), 0.1340</td>
<td></td>
</tr>
</tbody>
</table>

P-value given is based on logrank test, stratified by adjuvant chemotherapy for each randomization option, and by randomization 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 drug 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 randomization 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 postmenopausal 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% patients of the 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 of 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 unblended 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 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) substudy (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 decrease 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 substudy.

Updated results (median duration of follow-up was 50 months) from the Lipid substudy (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% vs placebo 1.2%), thromboembolic events (letrozole 1.0%, placebo 0.6%) and cerebrovascular accident (letrozole 1.7% vs 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 postmenopausal women with advanced breast cancer. In 907 women, letrozole was superior to tamoxifen in time to progression (primary endpoint) and in overall objective response, time to treatment failure and clinical benefit.

The results are summarized in Table 5:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Statistic</th>
<th>Letrozole n=453</th>
<th>Tamoxifen n=454</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to progression</td>
<td>Median</td>
<td>9.4 months (8.9, 11.6 months)</td>
<td>6.0 months (5.4, 6.3 months)</td>
</tr>
<tr>
<td></td>
<td>(95% CI for median)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hazard ratio (HR)</td>
<td>0.72 (0.62, 0.83)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(95% CI for HR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Objective response rate (ORR)</td>
<td>CR+PR</td>
<td>145 (32%) (28, 36%)</td>
<td>95 (21%) (17, 25%)</td>
</tr>
<tr>
<td></td>
<td>(95% CI for rate)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Odds ratio (95% CI for odds ratio)</td>
<td>1.78 (1.32, 2.40)</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall clinical benefit rate</td>
<td>CR+PR+NC≥24 weeks</td>
<td>226 (50%) (1.24, 2.11)</td>
<td>173 (38%) (3.7, 6.1 months)</td>
</tr>
<tr>
<td></td>
<td>Odds ratio (95% CI for odds ratio)</td>
<td>1.62</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.0004</td>
<td></td>
</tr>
<tr>
<td>Time to treatment failure</td>
<td>Median</td>
<td>9.1 months (8.6, 9.7 months)</td>
<td>5.7 months (3.7, 6.1 months)</td>
</tr>
<tr>
<td></td>
<td>(95% for median)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hazard ratio (95% CI for HR)</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

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 crossover was virtually completed by 36 months. The median time to crossover was 17 months (letrozole to tamoxifen) and 13 months (tamoxifen to letrozole).

Letrozole treatment in the first-line therapy of advanced breast cancer resulted in a median overall survival of 34 months compared with 30 months for tamoxifen (log-rank test P=0.53, not significant). 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 versus 58% for the tamoxifen treatment group. The absence of an advantage for letrozole on overall survival could be explained by the crossover 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 postmenopausal 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 $t_{\text{max}}$ 1 hour fasted versus 2 hours fed; and mean $C_{\text{max}}$ 129 ± 20.3 nmol/litre fasted versus 98.7 ± 18.6 nmol/litre 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 postmenopausal volunteers, 88.2 ± 7.6% of the radioactivity was recovered in urine and 3.8 ± 0.9% in faeces. At least 75% of the radioactivity recovered in urine up to 216 hours (84.7 ± 7.8% of the dose) was attributed to the glucuronide of the carbinol metabolite, about 9% to two unidentified metabolites, and 6% to unchanged letrozole.

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 $t_{1/2}$ 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 2000 mg/kg. In dogs letrozole caused signs of moderate toxicity at 100 mg/kg.

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

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

In a 104-week rat carcinogenicity study, no treatment-related 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 foetal 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
Tablets core:
- Silica, colloidal anhydrous
- Lactose monohydrate
- Microcrystalline cellulose
- Croscarmellose sodium
- Magnesium stearate

Tablet coating:
- Hypromellose (E464)
- Titanium dioxide (E171)
- Polysorbate 80 (E433)
- Iron oxide yellow (E172)
- Iron oxide red (E172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
18 months

6.4 Special precautions for storage
This product does not require any special temperature storage conditions. Store in original package.

6.5 Nature and contents of container
PVC/PE/PVdC Aluminum blisters. Packs of 14, 28, 30 or 100 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
PLIVA Pharma Limited
Vision House, Bedford Road, Petersfield, Hampshire, GU32 3QB

8 MARKETING AUTHORISATION NUMBER(S)
PL 10622/0339
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16/06/2009

10 DATE OF REVISION OF THE TEXT
16/06/2009
Module 3

The Patient Information Leaflet (PIL) below is the leaflet agreed at the end of the decentralised procedure. The marketing authorisation holder is not intending to market the product at the present time and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PIL and labelling for review to the regulatory authority before marketing the product.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Letrozole 2.5mg Film-coated Tablets

To be completed nationally

Letrozole

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 gets 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 is and what it is used for
2. Before you take Letrozole
3. How to take Letrozole
4. Possible side effects
5. How to store Letrozole
6. Further information

1. WHAT LETROZOLE 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

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 Letrozole listed in section 6 of this leaflet
- if you still have periods, i.e. if you have not yet gone through the menopause
- if you are pregnant
- if you 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
- if you have a severe liver disease
- if you have a history of osteoporosis 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.

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.

Children and adolescents (below 18 years)
Children and 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.

Pregnancy and breast-feeding mothers
You must not take Letrozole if you are pregnant or breast-feeding as it may harm your baby.
Since Letrozole is only recommended for postmenopausal women, pregnancy and breast-feeding restrictions most likely will not apply to you.
However, if you recently became postmenopausal or if you are premenopausal, your doctor should discuss with you about the necessity of a pregnancy test before taking Letrozole and of a 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
Letrozole contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE LETROZOLE

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’.

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 between 1 to 100 in every 10,000 patients):
- 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 discoloration, 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 swelling mainly of the face and throat (signs of allergic reaction) during treatment with Letrozole.

If any of the above occur, tell your doctor straight away.

Some side effects are very common. These side effects may affect more than 10 in every 100 patients.
- Hot flushes
- Fatigue
- Increased sweating
- Pain in bones and joints (arthritis)

If any of these affects you severely, tell your doctor.

Some side effects are common. These side effects may affect between 1 to 10 in every 100 patients.
- 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 between 1 to 10 in every 1,000 patients.
- 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 level of cholesterol (hypercholesterolemia) or high level of liver enzymes.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE LETROZOLE

Keep out of the reach and sight of children.

This medicinal product does not require any special temperature storage conditions. Store in the original package.

Do not take this medicine after the expiry date which is stated on the carton and blister. The expiry date refers to the last date of that month.

Do not dispose of any of your medicines via wastewater or household waste as they can be very harmful to the environment. Ask your pharmacist how to dispose of medicines no longer required.

6. FURTHER INFORMATION

What Letrozole contains
- The active substance is letrozole. Each film-coated tablet contains 2.5mg of letrozole.
- The other ingredients are
- Tablet core: silica, colloidal anhydrous, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate
- Tablet coating: hypromellose (E464), titanium dioxide (E171), polysorbate 80 (E433), iron oxide yellow (E172) and iron oxide red (E172).

What Letrozole film coated tablets look like and contents of the pack
The tablets are ochre, round, biconvex, film-coated tablets with ‘LT’ imprinted on one side and ‘2’ on the other side. Available in blister packs of 10, 14, 28, 30, 10 x 10 (bundle packs), 100 or 200 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

To be completed nationally

PLIVA-Lachema a.s., Bmo, Czech Republic or
AWD.pharma GmbH & Co KG, Radebeul, Germany

This medicinal product is authorised in the Member States of the EEA under the following names:

To be completed nationally when relevant.

UK: Letrozole 2.5mg Film-coated Tablets
BG: Letrozole Pliva
CZ: Letrozol Pliva 2.5mg
DE: Letrozol AWD 2.5 mg Filmtabletten
ES: LETROZOL EDIGEN 2.5 mg comprimidos recubiertos con película
HU: Letrozol Pliva 2.5mg filmtabletta
IE: Femestin(TBA)
PL: Letrozole PLIVA
RO: Letrozol PLIVA 2.5mg
SI: Letrozol Pliva 2.5mg filmsko obložene tablete
SK: Letrozol PLIVA

This leaflet was last approved in {MM/YYYY}.

To be completed nationally
## Module 4
### Labelling

The labelling below is the label agreed at the end of the decentralised procedure. The marketing authorisation holder is not intending to market the product at the present time and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PIL and labelling for review to the regulatory authority before marketing the product.

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARTON</td>
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</table>

### 1. Name of the medicinal product

Letrozole 2.5mg film-coated Tablets

Letrozole

### 2. Statement of active substance(s)

Each tablet contains 2.5mg of letrozole

### 3. List of excipients

Contains lactose monohydrate. See package leaflet for further information.

### 4. Pharmaceutical form and contents

14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
100 film-coated tablets

### 5. Method and route(s) of administration

For oral use. Read the package leaflet before use.

### 6. Special warning that the medicinal product must be stored out of the reach and sight of children

Keep out of the reach and sight of children.

### 7. Other special warning(s), if necessary

### 8. Expiry date

EXP.

### 9. Special storage conditions

This medicinal product does not require any special temperature storage condition. Store in the original package.
<p>| 10. | SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE |
| 11. | NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER |
| 12. | to be completed nationally |
| 13. | MARKETING AUTHORISATION NUMBER(S) |
| 14. | to be completed nationally |
| 15. | BATCH NUMBER |
| 16. | GENERAL CLASSIFICATION FOR SUPPLY |
| 17. | Medicinal product subject to medical prescription |
| 18. | INSTRUCTIONS ON USE |
| 19. | INFORMATION IN BRAILLE |
| 20. | UK Letrozole 2.5mg film-coated Tablets |
| 21. | to be completed nationally |</p>
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLISTER</td>
</tr>
</tbody>
</table>

| 1. NAME OF THE MEDICINAL PRODUCT                  |
| to be completed nationally                        |
| UK: Letrozole 2.5mg film-coated Tablets           |
| Letrozole                                         |

| 2. NAME OF THE MARKETING AUTHORISATION HOLDER     |
| to be completed nationally                        |

| 3. EXPIRY DATE                                    |
| EXP.                                              |

| 4. BATCH NUMBER                                   |
| Batch                                             |

| 5. OTHER                                          |

Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Bulgaria, the Czech Republic, Germany, Hungary, Ireland, Poland, Romania, Spain, Slovenia, the Slovak Republic and the UK considered that the application for Letrozole 2.5mg Film-Coated Tablets could be approved. This product is a prescription only medicine (POM) for the following indications:

- Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.
- Extended adjuvant treatment of hormone-dependent early breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy for 5 years.
- First-line treatment in postmenopausal 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.

This application for Letrozole 2.5mg Film-Coated Tablets is submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Femara 2.5mg Film-Coated Tablets, which was originally approved in the UK to Ciba-Geigy PLC on 18th November 1996.

The active substance, letrozole, is a reversible (Type II), non-steroidal 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.

No new preclinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies with the exception of the bioequivalence study have been performed and none are required for this application as the pharmacology of letrozole is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or 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.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Letrozole 2.5mg Film-Coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Letrozole</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Enzyme inhibitor. Non-steroidal aromatase inhibitor (inhibitor of oestrogen biosynthesis); antineoplastic agent (L02B G04)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>2.5mg Film-Coated Tablets</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/1367/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Bulgaria, the Czech Republic, Germany, Hungary, Ireland, Poland, Romania, Spain, Slovenia, the Slovak Republic</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 10622/0339</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>PLIVA Pharma Limited Vision House Bedford Road Petersfield, Hampshire GU32 3QB</td>
</tr>
</tbody>
</table>
III  SCIENTIFIC OVERVIEW AND DISCUSSION
III.1  QUALITY ASPECTS
S.  Active substance

INN: Letrozole
Chemical name: Benzonitrile, 4,4’-(1H-1,2,4-triazol-1-ylmethylene)bis-
        4,4’-(1H-1,2,4-Triazol-1-ylmethylene) dibenzonitrile

Structural formula:

\[
\begin{align*}
\text{Letrozole} \\
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{NC} \quad \text{NC}
\end{array}
\end{align*}
\]

Molecular formula: C\(_{17}\)H\(_{11}\)N\(_5\)
Molecular weight: 285.31 g/mol
Appearance: White to yellowish crystalline powder
Solubility: Practically insoluble in water, freely soluble in methylene chloride and sparingly soluble in methanol.

Letrozole is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance letrozole, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.
P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients colloidal anhydrous silica, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate. The tablet coating contains hypromellose (E464), titanium dioxide (E171), polysorbate 80 (E433), iron oxide yellow (E172), iron oxide red (E172).

All excipients in the tablet core comply with their relevant European Pharmacopoeia monographs. All excipients in the tablet coating comply with their relevant European Pharmacopoeia monographs, with the exception of iron oxide yellow (E172) and iron oxide red (E172), which comply with the French National Formulary.

None of the excipients used contain material of animal or human origin, with the exception of lactose monohydrate. The supplier of lactose monohydrate has confirmed that the lactose used is sourced from healthy animals under the same conditions as milk for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to produce products that could be considered generic medicinal products of Femara 2.5mg Film-Coated Tablets (Ciba-Geigy PLC).

The reference product used in the bioequivalence study is qualitatively and quantitatively identical to the reference product.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished products versus the reference products of Femara 2.5mg Film-Coated Tablets (Ciba-Geigy PLC).

Comparative in vitro dissolution profiles have been provided for the proposed and originator product.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data has been provided.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for all working standards used.

Container-Closure System

The finished product is packaged in blisters consisting of polyvinyl chloride, polyethylene, polyvinylidene chloride and aluminium. The product is packaged in sizes of 14, 28, 30 and 100 tablets.
Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on two full-scale batches of the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 18 months, with storage instructions ‘Store in original package’. This product does not require any special temperature storage conditions.

Suitable post approval stability commitments have been provided to follow-up the batches from the current studies and to place future batches on stability.

**Bioequivalence/bioavailability**
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

**Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels**
The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**MAA forms**
The MAA form is pharmaceutically satisfactory.

**Expert report**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**
The grant of a marketing authorisation is recommended.

**III.2 PRE-CLINICAL ASPECTS**
Pharmacodynamic, pharmacokinetic and toxicological properties of letrozole are well-known. As letrozole is a widely used, well-known active substance, no further studies are required and the applicant has provided none. The applicant’s non-clinical overview is satisfactory, providing and appropriate review of the drug’s pharmacology and toxicology.

**III.3 CLINICAL ASPECTS**
1. **Introduction**
This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. For more details, the reader should refer to the company's clinical overview and summary and to the clinical file.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.
2. **Clinical study reports**

To support these applications, the marketing authorisation holder has submitted one single dose bioequivalence study.

**Open-label, 2-way crossover, single dose bioequivalence study of Letrozole 2.5mg Tablets and Femara® 2.5mg Tablets, (Novartis S.R.O.) in healthy, non-smoking male and post-menopausal or surgically sterile female subjects under fasting conditions.**

All subjects were in a fasted state before dosing. Blood sampling was performed pre- and then over a 120 hour post-dose treatment period. There was a washout period of at least 4 weeks. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng/ml/h)</th>
<th>AUC_{0-∞} (ng/ml/h)</th>
<th>C_{max} (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Letrozole:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>1102.38±273.02</td>
<td>1517.60±586.73</td>
<td>-</td>
</tr>
<tr>
<td>Reference</td>
<td>1054.85±243.02</td>
<td>1460.56±555.30</td>
<td>-</td>
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<tr>
<td><strong>Intra-Subject CV</strong></td>
<td>7.95%</td>
<td>-</td>
<td>12.04%</td>
</tr>
<tr>
<td><strong>Ratio (90% CI)</strong></td>
<td>103.26 (99.18 to 107.51%)</td>
<td>104.54 (87.46 to 124.95)</td>
<td>101.01 (95.40 to 106.94 %)</td>
</tr>
</tbody>
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The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t} and C_{max} for letrozole lie within 80-125% boundaries. Thus, bioequivalence has been shown between the test and reference products in this study.

**Efficacy**

No new data on the efficacy of letrozole are submitted and none are required for this type of application.

**Safety**

No new safety concerns were raised from the adverse events occurring in each bioequivalence study. No other new safety data were submitted with this application and none were required.

**SPC, PIL, Labels**

The SPC, PIL and labels are medically acceptable. The SPCs are consistent with that for the originator products.

**Conclusion**

The grant of a marketing authorisation is recommended.

**IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**

**QUALITY**

The important quality characteristics of Letrozole 2.5mg Film-Coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

**PRECLINICAL**

No new preclinical data were submitted and none are required for an application of this type.
EFFICACY
Bioequivalence has been demonstrated between the applicant’s Letrozole 2.5mg Film-Coated Tablets and the originator product Femara 2.5mg Film-Coated Tablets (Ciba-Geigy PLC).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with letrozole is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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