Public Assessment Report

Decentralised Procedure

Letrozole 2.5mg Film-coated Tablets

(Letrozole)

UK/H/1654/01/DC

UK licence numbers: PL 17871/0036

Jenson Pharmaceutical Services Limited
LAY SUMMARY

On 15th February 2010, the MHRA granted Jenson Pharmaceutical Services Limited a Marketing Authorisation (licence) for the medicinal product Letrozole 2.5mg film-coated tablets (PL 17871/0036, UK/H/1654/01/DC). This is a prescription-only medicine (POM).

The active ingredient, 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 levels 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. Letrozole is used to treat breast cancer in post-menopausal women only. It can be used along with other treatment or taken alone. It can also be used to treat breast cancer before breast surgery.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of Letrozole 2.5mg film-coated tablets outweigh the risks and a Marketing Authorisation was granted.
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Module 1

Information about Initial Procedure

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Letrozole 2.5mg film-coated tablets</th>
</tr>
</thead>
<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>
</tbody>
</table>
| MA Holder                     | Jenson Pharmaceutical Services Limited  
|                               | Carradine House                     |
|                               | 237 Regents Park Road               |
|                               | London                              |
|                               | N3 3LF                              |
|                               | United Kingdom                      |
| Reference Member State (RMS)  | UK                                  |
| Concerned Member State / s (CMS) | SK                                |
| Procedure Numbers             | UK/H/1654/01/DC                     |
| Timetable                     | End of Procedure – 1st February 2010 |
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 tablet contains 2.5 mg of letrozole
Each film-coated tablet contains 61.53 mg lactose monohydrate. For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated Tablet
Letrozole 2.5 mg Film-coated Tablets are dark yellow, capsule-shaped, slightly biconvex, debossed with “LZ 2.5” on one side and “G” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.
Treatment of early invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy.
First-line treatment in postmenopausal women with advanced breast cancer.
Advanced breast cancer in postmenopausal women in whom tamoxifen or other anti-oestrogen therapy has failed.
Pre-operative therapy in postmenopausal women with localised hormone receptor positive breast cancer, to allow subsequent breast-conserving surgery in women not originally considered candidates for breast-conserving surgery. Subsequent treatment after surgery should be in accordance with standard of care.

4.2 Posology and method of administration
Adult and elderly patients
The recommended dose of Letrozole is 2.5 mg once daily. In the adjuvant setting, treatment with Letrozole should continue for 5 years or until tumour relapse occurs, whichever comes first. Following standard adjuvant tamoxifen therapy, treatment with Letrozole should continue for 4 years or until tumour relapse occurs, whichever comes first. Currently there is a lack of long-term data, therefore the optimal duration of therapy has not yet been established. In patients with metastatic disease, treatment with Letrozole should continue until tumour progression is evident. Regular monitoring to observe progression during the pre-operative treatment period is recommended (see Section 5.1). No dose adjustment is required for elderly patients.

Children
Not recommended for use in children.

Patients with hepatic and/or renal impairment
No dosage adjustment is required for patients with mild to moderate hepatic impairment (Child-Pugh grade A and B) or renal impairment (creatinine clearance \( \geq 10 \) mL/min.), (see section 5.2).

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
Premenopausal, pregnant or lactating women (see section 4.6).
Patients with severe hepatic impairment (Child-Pugh grade C).
Pre-operative use of letrozole is contraindicated if the receptor status is negative or unknown.
4.4 Special warnings and precautions for use

Letrozole is not recommended for use in children, as efficacy and safety in this patient group have not been assessed in clinical studies. There are no efficacy data to support the use of Letrozole in men with breast cancer.

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

As Letrozole is a potent oestrogen-lowering agent, reductions in bone mineral density can be anticipated. The impact of Letrozole on long-term fracture risk remains undetermined. During adjuvant treatment with Letrozole, women with osteoporosis or at risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry e.g. DEXA scanning at the commencement of treatment. Although adequate data to show the effects of therapy in the treatment of the bone mineral density loss caused by Letrozole are not available, treatment for osteoporosis should be initiated as appropriate and patients treated with Letrozole should be carefully monitored.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or 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 coadministration of Letrozole with these drugs does not result in clinically significant drug interactions, even though cimetidine is a known inhibitor of one of the cytochrome P450 isoenzymes capable of metabolising letrozole in vitro (see also section 5.2).

There was no evidence of other clinically relevant interaction in patients receiving other commonly prescribed drugs (e.g. benzodiazepines; barbiturates; NSAIDs such as diclofenac sodium, ibuprofen; paracetamol; furosemide; omeprazole).

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

Letrozole inhibits in vitro the cytochrome P450-isoenzymes 2A6 and moderately 2C19, however, CYP2A6 does not play a major role in drug metabolism. In in vitro experiments letrozole was not able to substantially inhibit the metabolism of diazepam (a substrate of CYP2C19) at concentrations approximately 100-fold higher than those observed in plasma at steady-state. Thus, clinically relevant interactions with CYP2C19 are unlikely to occur. Nevertheless, 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

Pregnancy

Letrozole is contraindicated during pregnancy (see section 4.3).

Lactation

Letrozole is contraindicated during lactation (see section 4.3).

Women of child-bearing potential

The physician needs to discuss the necessity of adequate contraception with women who have the potential to become pregnant including women who are perimenopausal or who have recently become postmenopausal, until their postmenopausal status is fully established.

There are no adequate data from the use of Letrozole in pregnant women.

Embryotoxicity and foetotoxicity were seen in pregnant rats following oral administration of letrozole, and there was an increase in the incidence of foetal malformation among the animals treated. However, it is not known whether this was an indirect consequence of the pharmacological activity of letrozole (inhibition of oestrogen biosynthesis) or a direct drug effect.

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, as adjuvant treatment of early breast cancer as well as in the treatment of women who have received prior standard tamoxifen therapy. Approximately one third of the patients treated with letrozole in the metastatic and neoadjuvant settings, approximately 70-75% of the patients in the adjuvant setting (both letrozole and tamoxifen arms), and approximately 40% of the patients treated following standard adjuvant tamoxifen (both letrozole and placebo arms) experienced adverse reactions. Generally, the observed adverse reactions are mainly mild or moderate in nature, and most are associated with oestrogen deprivation.

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, 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 adverse events was observed. The incidence of self-reported osteoporosis, any time after randomisation was higher in patients who received letrozole than in patients who received placebo (12.3 % vs. 7.4 %). The incidence of clinical fractures, at any time after randomisation, was higher in patients who received letrozole than for placebo patients (10.9 % vs. 7.2 %). 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.

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

| Table 1 |
|---------------------------------|---------------------------------|
| **Infections and infestations** | Urinary tract infection         |
| Uncommon:                       |                                 |
| **Neoplasms, benign, malignant and unspecified (including cysts and polyps)** | Tumour pain [6]                |
| Uncommon:                       |                                 |
| **Blood and the lymphatic system disorders** | Leucopenia                     |
| Uncommon:                       |                                 |
| **Immune system disorders**     |                                 |
| Not known:                      | Angioedema, anaphylactic reactions |
| **Metabolism and nutrition disorders** | Anorexia, appetite increase, raised serum cholesterol |
| Common:                         | General oedema                  |
| Uncommon:                       |                                 |
| **Psychiatric disorders**       | Depression                      |
| Common:                         | Anxiety [1]                     |
| Uncommon:                       |                                 |
| **Nervous system disorders**    | Headache, dizziness             |
| Common:                         | Somnolence, insomnia, memory impairment, dyssomnia [2], taste disturbance, cerebrovascular accident |
| Uncommon:                       |                                 |
| **Eye disorders**               | Cataract, eye irritation, blurred vision |
| Uncommon:                       |                                 |
| **Cardiac disorders**           | Palpitations, tachycardia        |
| Uncommon:                       |                                 |
| **Vascular disorders**          | Thrombophlebitis [11], hypertension, ischemic cardiac events [7] |
| Uncommon:                       | Pulmonary embolism, arterial thrombosis, cerebrovascular infarction |
| **Respiratory, thoracic and mediastinal disorders** | Dyspnoea, cough |
| Uncommon:                       |                                 |
| **Gastrointestinal disorders**  | Nausea, vomiting, dyspepsia, constipation, diarrhoea |
| Uncommon:                       | Abdominal pain, stomatitis, dry mouth |
| **Hepatobiliary disorders**     | Increased hepatic enzymes        |
| Uncommon:                       |                                 |
Skin and subcutaneous tissue disorders

Common: Alopecia, increased sweating, rash (4)
Uncommon: Pruritus, dry skin, urticaria

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
Common: Fatigue (5), peripheral oedema
Uncommon: Pyrexia, mucosal dryness, thirst

Investigations

Common: Weight increase
Uncommon: Weight loss

*(Including:

(1) Including nervousness, irritability
(2) Including paraesthesia, hypoaesthesia
(3) Including superficial and deep thrombophlebitis
(4) Including erythematous, maculopapular, psoriaform and vesicular rash
(5) Including asthenia and malaise
(6) In metastatic/neoadjuvant setting only
(7) In the adjuvant setting, irrespective of causality, the following adverse events occurred in the letrozole and tamoxifen groups respectively: thromboembolic events (1.2% vs. 3.0%), angina pectoris (0.8% vs. 0.8%), myocardial infarction (0.5% vs. 0.4%), cardiac failure (0.8% vs. 0.3%).

Table 2 presents the frequency of pre-specified adverse events grades 1-5 in the BIG 1-98 study, irrespective of causality, reported in patients receiving trial therapy and up to 30 days after cessation of trial therapy.

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-specified event</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Hot flashes / hot flushes</td>
</tr>
<tr>
<td>Arthralgia / arthritis</td>
</tr>
<tr>
<td>Night sweats</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Fatigue (lethargy, malaise, asthenia)</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
</tr>
<tr>
<td>Myalgia</td>
</tr>
<tr>
<td>Oedema</td>
</tr>
<tr>
<td>Bone fractures</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Vaginal irritation</td>
</tr>
<tr>
<td>Dizziness/light-headedness</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Total serum cholesterol &gt; 1.5 x ULN1,2</td>
</tr>
<tr>
<td>Thromboembolic event</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Cerebrovascular accident/transient ischemic attack</td>
</tr>
<tr>
<td>Breast pain</td>
</tr>
<tr>
<td>Cataract</td>
</tr>
<tr>
<td>Endometrial hyperplasia or cancer3</td>
</tr>
<tr>
<td>Anorexia</td>
</tr>
</tbody>
</table>
Angina pectoris (new, or worsening or requiring surgical intervention) | 30 (0.8) | 30 (0.8)  
Cardiac failure | 32 (0.8) | 13 (0.3)  
Myocardial infarction | 20 (0.5) | 15 (0.4)  
Ovarian cyst | 18 (0.5) | 16 (0.4)  

1. Based on number of patients with normal serum cholesterol levels at baseline, and developing at least one value greater than 1.5 times the upper limit of normal in the laboratory measuring total serum cholesterol. Approximately 90% of the measured values were non-fasting measurements.

2. Denominator is number of patients with baseline measurements of total serum cholesterol – letrozole, n=3207; tamoxifen, n=3228

3. Denominator is number of patients not having undergone hysterectomy at baseline – letrozole, n=3090; tamoxifen, n=3157

4.9 Overdose

There is no clinical experience of overdosage. In animal studies, letrozole exhibits only a slight degree of acute toxicity. In clinical trials, the highest single and multiple dose tested in healthy volunteers was 30 mg and 5 mg, respectively, the latter also being the highest dose tested in postmenopausal breast cancer patients. Each of these doses was well tolerated. There is no clinical evidence for a particular dose of letrozole resulting in life-threatening symptoms.

There is no specific antidote to letrozole. In general, supportive care, symptomatic treatment and frequent monitoring of vital signs is appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Pharmacodynamic effects

The elimination of oestrogen-mediated stimulatory effects is a prerequisite for tumour response in cases where the growth of tumour tissue depends on the presence of oestrogens. 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 cytochrome P450 subunit of the enzyme, resulting in a reduction of oestrogen biosynthesis in all tissues.

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-deoxycortisol, 17-hydroxy-progesterone, 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.

**Adjuvant treatment**

A multicentre, double-blind study randomised over 8000 postmenopausal women with resected receptor-positive early breast cancer, to one of the following arms:

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

Data in Table 3 reflect results from non-switching arms (arms A and B) together with data truncated 30 days after the switch in the two switching arms (arms C and D). 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 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. 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; \(P=0.044\)) and in node positive patients (hazard ratio 0.71; \(P=0.0002\)). A significant benefit of letrozole over tamoxifen is not yet evident in node negative patients (hazard ratio 0.98; \(P=0.888\)).

There was no significant difference between treatments in overall survival (hazard ratio 0.86; \(P=0.155\)). Table 3 summarises the results.

<table>
<thead>
<tr>
<th>Table 3 Disease-free survival and overall survival (ITT population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Table content]</td>
</tr>
</tbody>
</table>

**Treatment after standard adjuvant tamoxifen**

In a multicentre, double-blind, randomised, placebo-controlled study, performed in over 5100 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% of the patients being followed-up for up to 38 months) showed that letrozole reduced the risk of recurrence by 42% compared with placebo (hazard ratio 0.58; \(P=0.00003\)), an absolute reduction of 2.4%. This statistically significant benefit in DFS in favour of letrozole was observed regardless of nodal status or prior chemotherapy.

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; \(P=0.29\)).
Table 4 summarises the results:

<table>
<thead>
<tr>
<th></th>
<th>Letrozole N=2582</th>
<th>Placebo N=2586</th>
<th>Hazard Ratio (95 % CI)</th>
<th>P -Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease-free survival</strong> (primary)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- events (protocol definition, total)</td>
<td>92 (3.6%)</td>
<td>155 (6.0%)</td>
<td>0.58 (0.45, 0.76)</td>
<td>0.00003</td>
</tr>
<tr>
<td><strong>Distant disease-free survival</strong></td>
<td>57</td>
<td>93</td>
<td>0.61 (0.44, 0.84)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Overall survival</strong> (secondary)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- number of deaths (total)</td>
<td>51</td>
<td>62</td>
<td>0.82 (0.56, 1.19)</td>
<td>0.291</td>
</tr>
<tr>
<td><strong>Contralateral breast cancer</strong> (secondary)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- including DCIS/LCIS</td>
<td>19</td>
<td>30</td>
<td>0.63 (0.36, 1.13)</td>
<td>0.120</td>
</tr>
<tr>
<td>- invasive</td>
<td>15</td>
<td>25</td>
<td>0.60 (0.31, 1.14)</td>
<td>0.117</td>
</tr>
</tbody>
</table>

CI = confidence interval, DCIS = ductal carcinoma in situ, LCIS = lobular carcinoma in situ
1 Stratified by receptor status, nodal status and prior adjuvant chemotherapy
2 Non-stratified analysis
3 Odds ratio, non-stratified analysis

Updated 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. After the unblinding of the study, 56% of the patients in the placebo arm opted to switch to letrozole.

In this analysis of DFS, letrozole significantly reduced the risk of breast cancer recurrence compared with placebo (HR 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 (OR 0.59; 95% CI 0.36, 0.96; P=0.03). There was no significant difference in distant disease-free survival or overall survival.

The clinical interpretation of these updated analyses should take into account that over half of the patients in the placebo arm switched to letrozole. Therefore, analyses were conducted to evaluate the effect of the switch. In one exploratory analysis comparing letrozole with placebo until switch, letrozole reduced the risk of breast cancer recurrence (HR 0.55; 95% CI 0.45,0.68; p < 0.001).

After unblinding, patients who switched to letrozole from placebo had been off adjuvant tamoxifen for a median 31 months (range 14 to 79 months). Other analyses were performed within the placebo arm taking account of the switch to letrozole. Acknowledging the varying times of the switch after the completion of prior tamoxifen therapy and the known limitations of non-randomised comparison, results suggested a consistent reduction in the risk of breast cancer recurrence in those patients who switched to letrozole (HR 0.31; 95% CI 0.20, 0.49, p < 0.001).

The efficacy of letrozole was not assessed in women who discontinued tamoxifen therapy more than 3 months earlier.

There was no difference in safety and efficacy between patients aged < 65 versus ≥ 65 years.

Updated results (median follow-up was 40 months) from the bone mineral density (BMD) sub-study (n=226) demonstrated that, at 2 years, compared to baseline, patients receiving letrozole had a median decrease of 3.8 % in hip BMD compared to 2.0 % in the placebo group (P=0.018). There was no significant difference in changes in lumbar spine BMD at any time. Concomitant calcium and vitamin D supplementation was mandatory in the BMD substudy. Updated results (median follow-up was approximately 50 months) from the lipid sub-study (n=347) showed no significant difference between the letrozole and placebo groups at any time. In the core study the incidence of cardiovascular ischemic events for letrozole versus placebo until switch was 11.1 % vs. 8.6 %.

**First-line treatment**

One large well-controlled double-blind trial was conducted comparing letrozole 2.5 mg to tamoxifen 20 mg daily as first-line therapy in postmenopausal women with locally advanced or metastatic breast cancer. In this trial of 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 (CR+PR+NC ≥ 24 weeks).

Letrozole treatment in the first line therapy of advanced breast cancer patients is associated with an early survival advantage over tamoxifen. A significantly greater number of patients were alive on letrozole versus tamoxifen throughout the first 24 months of the study. As the study design allowed patients to cross over upon progression to the other therapy the long-term survival could not be evaluated.
Pre-operative treatment
A double blind trial was conducted in 337 postmenopausal breast cancer patients randomly allocated either letrozole 2.5mg for 4 months or tamoxifen for 4 months. At baseline all patients had tumours stage T2-T4c, N0-2, M0, ER and/or PgR positive and none of the patients would have qualified for breast-conserving surgery. There were 55% objective responses in the letrozole treated patients versus 36% for the tamoxifen treated patients (p < 0.001) based on clinical assessment. This finding was consistently confirmed by ultrasound (p=0.042) and mammography (p < 0.001) giving the most conservative assessment of response. This response was reflected in a statistically significantly higher number of patients in the letrozole group who became suitable for and underwent breast-conserving therapy (45% of patients in the letrozole group versus 35% of patients in the tamoxifen group, p=0.022). During the 4-month pre-operative treatment period, 12% of patients treated with letrozole and 17% of patients treated with tamoxifen had disease progression on clinical assessment.

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 tmax: 1 hour fasted versus 2 hours fed; and mean Cmax: 129 ± 20.3 nmol/L fasted versus 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 14C-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 (CLm= 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 in vitro, but their individual contributions to letrozole clearance in vivo have not been established. In an interaction study co-administration with cimetidine, which is known to inhibit only the 3A4 isoenzyme, did not result in a decrease in letrozole clearance suggesting that in vivo the 2A6 isoenzyme plays an important part in total clearance. In this study a slight decrease in AUC and increase in Cmax were observed.

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 14C-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 volunteers with varying degrees of renal function (24 hour creatinine clearance 9-116 mL/min) no effect on the pharmacokinetics of letrozole or the urinary excretion of the glucuronide of its carbinol metabolite was found after a single dose of 2.5 mg. The Cmax, AUC and half-life of the metabolite have not been determined. In a similar study involving subjects with varying degrees of hepatic function, the mean AUC values of the volunteers with moderate hepatic impairment was 37 % higher than in normal subjects, but still within the range seen in subjects without impaired function.
5.3 Preclinical safety data

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 can be attributed to the pharmacological action of the compound. Effects on the liver (increased weight, hepatocellular hypertrophy, fatty changes) were observed, mainly at high dose levels. Increased incidences of hepatic vacuolation (both sexes, high dose) and necrosis (intermediate and high dose females) were also noted in rats treated for 104 weeks in a carcinogenicity study. They may have been associated with the endocrine effects and hepatic enzyme-inducing properties of letrozole. However, a direct drug effect cannot be ruled out.

In a 104-week mouse carcinogenicity study, dermal and systemic inflammation occurred, particularly at the highest dose of 60 mg/kg, leading to increased mortality at this dose level. Again it is not known whether these findings were an indirect consequence of the pharmacological activity of letrozole (i.e. linked to long-term oestrogen deprivation) or a direct drug effect.

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

In the carcinogenicity studies no treatment-related tumours were noted in male animals. In female animals, treatment-related changes in genital tract tumours (a reduced incidence of benign and malignant mammary tumours in rats, an increased incidence of benign ovarian stromal tumours in mice) were secondary to the pharmacological effect of the compound.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Sodium starch glycolate
Lactose monohydrate
Corn starch
Microcrystalline cellulose
Colloidal silicon dioxide
Magnesium stearate

Tablet Coating
Iron oxide yellow  E172
Iron oxide red  E172
Hypermellose
Polydextrose
Polyethylene glycol
Quinoline Yellow
Triacetin
Titanium dioxide  E171

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC-PVdC / Aluminium foil blister strips in packages of 14, 28 and 30.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.
Module 3

Patient Information Leaflet – text version

PACKAGE LEAFLET: INFORMATION FOR THE USER

Letrozole 2.5 mg Film-coated Tablets
(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 side effect 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

Letrozole belongs to a group of medicines called aromatase inhibitors. It works by blocking the production of oestrogens. Letrozole is used to treat breast cancer in post-menopausal women only. It can be used along with other treatment or taken alone. It can also be used to treat breast cancer before breast surgery.

2. BEFORE YOU TAKE LETROZOLE

Do not take Letrozole if you
- are allergic (hypersensitive) to letrozole or any of the other ingredients in this medicine
- have not yet reached the menopause
- are pregnant or breast-feeding
- have serious liver problems.
Letrozole should only be used before breast surgery if the tumour is hormone-sensitive. Speak to your doctor if you know the tumour is not hormone-sensitive or you are unsure.

Take special care with Letrozole

You should tell your doctor before taking this medicine if you:
- have serious kidney problems
- know you have osteoporosis (weak or brittle bones) or are at risk of osteoporosis; your doctor will monitor your bone density before and during treatment.

This medicine is not suitable for children or men.

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
Letrozole should not be taken by pregnant or breast-feeding mothers as it could harm the baby. If you have just started the menopause and there is a chance you could become pregnant, talk to your doctor as you may need contraception. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Do not drive or operate machinery if you feel dizzy or drowsy while taking this medicine.

Important information about some of the ingredients of Letrozole
This medicine contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, such as lactose, contact your doctor before taking this medicine.

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.

Swallow the tablet whole with a glass of water.

The usual dose is:

Adults and the elderly
Take one 2.5 mg tablet daily.

Children
Letrozole should not be given to children.

If you take more Letrozole than you should
Contact your doctor or nearest hospital emergency department immediately. Take the container and any remaining tablets with you.

If you forget to take Letrozole
Take it as soon as you remember unless it is almost time for your next dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking Letrozole
Do not stop taking Letrozole without talking to your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Letrozole can cause side effects, although not everybody gets them.

If any of the following happen, stop taking Letrozole and tell your doctor immediately or go to your nearest hospital emergency department:
- an allergic reaction causing difficulty in breathing, tightness of the chest, swelling of the face, throat or tongue, or skin rashes
- if you suffer pain in the chest, spreading to your arms, neck, abdomen or back
- if you cough up blood, suffer from shortness of breath, chest pain or suffer unusual pain or swelling of your calf or leg
- if you suffer eyesight changes, numbness or weakness, and have difficulty speaking.
You may need urgent medical attention.
Very common side effects (affecting more than 1 in 10 people):
- hot flushes
- pain in the joints.

Common side effects (affecting fewer than 1 in 10 people):
- change in appetite, weight increase, raised cholesterol levels in the blood
- feeling depressed
- feeling dizzy, headache
- feeling or being sick, indigestion, constipation or diarrhoea
- hair loss, feeling sweaty, skin rashes
- muscle or bone pain, osteoporosis (weak or brittle bones), bone fractures
- feeling unusually tired or weak, swollen ankles or hands.

Uncommon side effects (affecting fewer than 1 in 100 people):
- urinary tract infection, passing more urine than usual
- pain in the breast (including in the tumour)
- reduction in white blood cells which can cause more infections than usual, fever, chills
- general swelling caused by fluid retention
- feeling anxious, nervous or irritable
- difficulty sleeping or feeling sleepy
- poor memory, ‘pins and needles’ sensation, change in taste
- irritable eyes, cataracts, blurred vision
- fast or irregular heart beat, missed beats, chest pain which may be severe, angina, heart attack
- raised blood pressure, severe headache, stroke, inflamed blood vessels
- breathlessness, cough
- abdominal pain, mouth ulcers, a dry mouth
- raised liver enzyme levels in the blood
- itchy dry or swollen skin
- arthritis (inflamed joints)
- vaginal dryness, bleeding or discharge
- fever, feeling thirsty
- weight loss.

Rare side effects (affecting fewer than 1 in 1000 people):
- clotting in a blood vessel (thrombosis)
- blood clot in the lung (pulmonary thrombosis).

If any side effect 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.
Do not use Letrozole after the expiry date, which is shown on the label or carton. The expiry date refers to the last day of that month.
This medicine has no special storage requirements.

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 contains

The active substance is letrozole 2.5 mg. The other ingredients are lactose monohydrate, microcrystalline cellulose, corn starch, colloidal silicon dioxide, sodium starch glycolate and magnesium stearate. The tablet coating contains iron oxides (E172), hypromellose, polydextrose, polyethylene glycol, triacetin, the colorant Aluminium Lake and titanium dioxide (E171).

What Letrozole looks like and contents of the pack

Your medicine comes as a dark yellow, capsule-shaped, coated tablet marked ‘LZ 2.5’ on one side and ‘G’ on the other. Letrozole is available in blister packs of 14, 28 and 30 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder:

Jenson Pharmaceutical Services Limited
Carradine House
237 Regents Park Road
London
N3 3LF
United Kingdom

Manufacturer:

McDermott Laboratories Limited (t/a Gerard Laboratories)
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13
Ireland

This leaflet was last approved in {MM/YYYY}.
Module 4
Labelling – text version
Carton text

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Cardboard Carton for PVC/PVdC – Aluminium Blisters

1. NAME OF THE MEDICINAL PRODUCT

Letrozole 2.5 mg Film-coated Tablets
letrozole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 2.5 mg letrozole

3. LIST OF EXCIPIENTS

Letrozole tablets contain lactose. Please see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30 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

[to be completed nationally]

9. SPECIAL STORAGE CONDITIONS
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
[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)
[To be completed nationally]

13. BATCH NUMBER
[To be completed nationally]

14. GENERAL CLASSIFICATION FOR SUPPLY
[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Letrozole 2.5 mg Film-coated Tablets
**Blister text**

| MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS |
| PVC/PVdC/Aluminium Blister Strips |

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Letrozole 2.5 mg Film-coated Tablets
   letrozole

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**
   
   [To be completed nationally]

3. **EXPIRY DATE**
   
   [To be completed nationally]

4. **BATCH NUMBER**
   
   [To be completed nationally]

5. **OTHER**
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Jenson Pharmaceutical Services Limited a Marketing Authorisation for the medicinal product Letrozole 2.5mg film-coated tablets (PL 17871/0036, UK/H/1654/01/DC) on 15th February 2010. The product is a prescription-only medicine.

This is an abridged application for Letrozole 2.5mg film-coated tablets, submitted under Article 10.1 of 2001/83 EC, as amended. The application refers to the UK reference product, Femara Tablets 2.5mg (PL 00101/0493), authorised to Novartis Pharmaceuticals UK Limited on 21st September 1997; as a Change of Ownership application from PL 00001/0224, originally authorised to Ciba-Geigy Plc on 18th November 1996. The reference product has been authorised in the UK for more than 10 years, so the period of data exclusivity has expired. With the UK as the Reference Member State in this Decentralised Procedure, Jenson Pharmaceutical Services Limited applied for a Marketing Authorisation for Letrozole 2.5mg film-coated tablets in Slovakia.

Letrozole 2.5mg film-coated tablets are indicated in the following:

- Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.
- Treatment of early invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy.
- First-line treatment in postmenopausal women with advanced breast cancer.
- Advanced breast cancer in postmenopausal women in whom tamoxifen or other anti-oestrogen therapy has failed.
- Pre-operative therapy in postmenopausal women with localised hormone receptor positive breast cancer, to allow subsequent breast-conserving surgery in women not originally considered candidates for breast-conserving surgery. Subsequent treatment after surgery should be in accordance with standard of care.

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 (ATC code: L02B G04). 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.

Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability: 99.9%). Plasma protein binding of letrozole is approximately 60%, mainly to albumin (55%). Metabolic clearance to a pharmacologically inactive carbinol metabolite is the major elimination pathway of letrozole (Cl\textsubscript{m}= 2.1 L/h) but is relatively slow when compared to hepatic blood flow (about 90 L/h). 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.

No new non-clinical or clinical efficacy studies were conducted, which is acceptable given that the application cross-refers to a product that has been licensed for over 10 years.

The application is supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Letrozole 2.5mg film-coated tablets, to that of the reference product, Femara 2.5mg tablets (Novartis). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. 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.

The RMS considers that the pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH 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.

The Marketing Authorisation holder (MAH) has provided adequate justification for not submitting a Risk Management Plan (RMP) and Environmental Risk Assessment (ERA). The lack of an Environmental Risk Assessment is justified since the application is for a generic version of an approved product and it is not likely to change the total market of letrozole.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th><strong>Name of the product in the Reference Member State</strong></th>
<th>Letrozole 2.5mg film-coated tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name(s) of the active substance(s) (INN)</strong></td>
<td>Letrozole</td>
</tr>
<tr>
<td><strong>Pharmacotherapeutic classification (ATC code)</strong></td>
<td>Non-steroidal aromatase inhibitor (L02B G04)</td>
</tr>
<tr>
<td><strong>Pharmaceutical form and strength(s)</strong></td>
<td>Film-coated tablets – 2.5mg</td>
</tr>
<tr>
<td><strong>Reference numbers for the Mutual Recognition Procedure</strong></td>
<td>UK/H/1654/01/DC</td>
</tr>
<tr>
<td><strong>Reference Member State</strong></td>
<td>United Kingdom</td>
</tr>
<tr>
<td><strong>Member States concerned</strong></td>
<td>SK</td>
</tr>
<tr>
<td><strong>Marketing Authorisation Number(s)</strong></td>
<td>PL 17871/0036</td>
</tr>
<tr>
<td><strong>Name and address of the authorisation holder</strong></td>
<td>Jenson Pharmaceutical Services Limited Carradine House 237 Regents Park Road London N3 3LF United Kingdom</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

Letrozole

Nomenclature:

INN: Letrozole

Chemical names:

i) Benzonitrile, 4,4’-(1H-1,2,4-triazol-1-ylmethylene)bis-

ii) 4,4’-(1H-1,2,4-Triazol-1-ylmethylene) dibenzonitrile

Structure:

![Structure of Letrozole](image)

Molecular formula: $\text{C}_{17}\text{H}_{11}\text{N}_5$

Molecular weight: 285.31 g/mol

CAS No: 112809-51-5

Physical form: White to yellowish crystalline powder

Solubility: Practically insoluble in water, freely soluble in methylene chloride and sparingly soluble in methanol

The active substance, letrozole, is the subject of a European Pharmacopoeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of letrozole are supported by an EDQM Certificate of Suitability (CEP). This certificate is accepted as confirmation of the suitability of letrozole for inclusion in this medicinal product.

The active substance is stored in appropriate packaging. The primary packaging is sealed low-density polyethylene, clear, colourless bags. The secondary packaging is sealed black polyethylene bags in HDPE drums. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary polyethylene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and no significant changes in any parameters were observed. The proposed retest period of 3 years is justified.
MEDICINAL PRODUCT

Description and Composition

The finished product is presented as dark yellow, capsule-shaped, slightly biconvex, film-coated tablets, debossed with “LZ 2.5” on one side and “G” on the other side.

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, colloidal silicon dioxide, corn starch, and magnesium stearate making up the tablet core; and hypromellose, polydextrose, polyethylene glycol, quinoline yellow, triacetin, titanium dioxide (E171), iron oxide yellow (E172), and iron oxide red (E172) constituting ‘Opadry II Yellow 40L92586’ which makes up the film coating. Appropriate justification for the inclusion of each excipient has been provided.

All excipients of the tablet core comply with their respective European Pharmacopoeia monographs. The film-coating, ‘Opadry II Yellow 40L92586’, complies with satisfactory in-house specifications; all of its constituents comply with their respective European Pharmacopoeia monographs with the exception of yellow and red iron oxides, quinoline yellow, and polydextrose for which monographs are not available. Confirmation has been provided that Opadry II Yellow 40L92586 complies with requirements of Directive 78/25/EC and 95/45/EC. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate is of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

There were no novel excipients used and no overages.

Dissolution and impurity profiles

Comparative dissolution and impurity data were provided for the test and appropriate reference products. The dissolution and impurity profiles were found to be similar, with all impurities within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. A process validation protocol has been provided. A commitment has been made by the MAH that process validation will be conducted on the first three commercial batches.

Finished product specification

The finished product specifications are provided for both release and shelf life and are satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory Certificates of Analysis are provided.
for two pilot scale batches of the product, which indicate that the batches are compliant with the proposed specification. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**

The finished product is licensed for marketing in PVC (polyvinylchloride) - PVdC (polyvinylidene chloride) / aluminium foil blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The product is packaged in carton pack sizes of 14, 28 and 30 film-coated tablets. The MA Holder has stated that not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. This medicinal product does not require any special storage conditions.

**Bioequivalence Study**

A bioequivalence study was presented comparing the test product, Letrozole 2.5mg film-coated tablets, to the reference product, Femara 2.5mg tablets (Novartis).

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

**Expert Report**

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Product Information**

The approved SmPC, and leaflet and labelling texts are satisfactory.

**Conclusion**

The drug product corresponds to the current EU definition of a generic medicinal product because it complies with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis, and considering the bioequivalence data provided, the applicant’s claim that Letrozole 2.5mg film-coated tablets is a generic medicinal product of Femara Tablets 2.5mg (Novartis Pharmaceuticals UK Limited) is justified.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. A Marketing Authorisation has therefore been granted.
III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable for this application for a generic version of a product that has been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of letrozole, which is a widely used and well-known active substance. The CV of the non-clinical expert has been supplied.

III.3 CLINICAL ASPECTS

INDICATIONS

Letrozole 2.5mg film-coated tablets are indicated in the following:

- Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.
- Treatment of early invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy.
- First-line treatment in postmenopausal women with advanced breast cancer.
- Advanced breast cancer in postmenopausal women in whom tamoxifen or other anti-oestrogen therapy has failed.
- Pre-operative therapy in postmenopausal women with localised hormone receptor positive breast cancer, to allow subsequent breast-conserving surgery in women not originally considered candidates for breast-conserving surgery. Subsequent treatment after surgery should be in accordance with standard of care.

The indications are consistent with those of the reference product and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

The recommended posology is 2.5 mg orally once daily. Full details concerning the posology are provided in the SmPC.

The posology is consistent with that for the reference product and is satisfactory.

TOXICOLOGY

No new data have been submitted and none are required for this type of application.

CLINICAL PHARMACOLOGY

The clinical pharmacology of letrozole is well known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application.

Pharmacokinetics – bioequivalence study

The application is supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profiles of Letrozole 2.5mg film-coated tablets (test), and Femara 2.5mg tablets - Novartis (reference). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis have been provided for both the test and reference product.

This was a randomised, open-label, two-treatment, two-period, two-sequence, single dose crossover bioavailability and bioequivalence study. The study was conducted in 18 healthy male and post-menopausal or surgically sterile, female subjects between the ages of 18 to 65 years old, under fasting conditions. Following a supervised overnight fast of at least 10 hours,
a single dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 4 weeks was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 336.0 hours after administration of test or reference product. Plasma levels of letrozole were detected by a validated HPLC method.

Assessor’s comment:
The study design is acceptable; the washout period is of an appropriate duration as is the sampling period. According to the literature and the product information for the Innovator product, food has a modest effect on the rate of absorption of letrozole, the extent of absorption is unchanged and it is not considered to be of clinical significance, therefore a bioequivalence study in fed subjects is not considered necessary.

The primary pharmacokinetic parameters for this study were $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% CI fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$.

Results:
Eighteen subjects entered the trial. One subject withdrew after the 96 hour blood draw post dose in Period II but the data was included in the PK and statistical analysis as there was sufficient data to allow a meaningful analysis. There were no serious or significant adverse events reported in the study and both formulations were well tolerated. Three subjects experienced a total of three AE: one after letrozole (headache), one after Femara (musculoskeletal pain) and one at the end of the study examination (decreased blood calcium). Only one AE was considered possibly related to study mediation. All AE resolved spontaneously.

The summary of the results of the bioequivalence study are tabulated below:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Least Squares Mean</th>
<th>90% CI (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Femara 2.5mg (Reference)</td>
<td>Letrozole 2.5mg (Test)</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>29.9 (19)</td>
<td>31.1 (23)</td>
</tr>
<tr>
<td>AUC$_{0-t}$</td>
<td>1535.4 (40)</td>
<td>1549.5 (44)</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$</td>
<td>1547.5 (30)*</td>
<td>1534.2 (28)*</td>
</tr>
</tbody>
</table>

* n=17
Conclusion on Bioequivalence

The results of the bioequivalence study show that the test and reference products are bioequivalent under fasting conditions as the confidence intervals for $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ for letrozole fall within the acceptance criteria range of 80-125% in line with current guidelines.

Clinical efficacy

No new data have been submitted and none are required. The reference product is established and the application depends upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of letrozole is well-established from its extensive use in clinical practice.

Clinical safety

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of letrozole is well-known.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPC is consistent with that for the reference product, and is acceptable.

Patient Information Leaflet

The PIL text is in line with the approved SmPC and is satisfactory.

Labelling

The labelling text is satisfactory.

Expert report

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

Periodic Safety Update Report (PSUR)

The applicant has applied for a PSUR submission upon approval on 31st October 2011 and as letrozole is a well known active substance which has been marketed for many years throughout the EU the suggestion is acceptable.

CONCLUSIONS

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (Letrozole 2.5mg film-coated tablets) and reference (Femara 2.5mg tablets - Novartis) products within general acceptance limits.

Sufficient clinical information has been submitted to support this application. A Marketing Authorisation was therefore granted.
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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Letrozole 2.5mg film-coated tablets, and the reference product, Femara 2.5mg tablets (Novartis).

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The SmPC, and PIL and labelling texts are satisfactory and consistent with those for the reference product.

A user consultation with target patient groups on the package information leaflet (PIL) text has been performed on the basis of a bridging report making reference to Tamoxifen 10 mg, 20 mg and 40 mg tablets. The bridging report submitted by the applicant has been found acceptable.

The Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for all packaging and PILs for assessment before packs are commercially marketed.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study, and other data provided, support the claim that the applicant’s Letrozole 2.5mg film-coated tablets is a generic version of Femara Tablets 2.5mg (Novartis Pharmaceuticals UK Limited). Extensive clinical experience with Letrozole is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit ratio is considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

There have been no variation applications submitted after approval of the initial procedure.

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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