LETROZOLE 2.5MG FILM-COATED TABLETS
PL 33410/0061

UKPAR

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LETROZOLE 2.5MG FILM-COATED TABLETS
PL 33410/0061

LAY SUMMARY

On 18th February 2010, the MHRA granted APSLA Limited a Marketing Authorisation (licence) for Letrozole 2.5mg Film-Coated Tablets (PL 33410/0061).

Letrozole 2.5mg Film-Coated Tablets contain letrozole which belongs to a group of medicines called aromatase inhibitors. These medicines act by blocking the production of oestrogens.

Letrozole 2.5mg Film-Coated Tablets are used in the treatment of breast cancer in post-menopausal women.
Letrozole 2.5mg Film-Coated Tablets can be used either before surgery to reduce the size of the tumour, or after surgery to help prevent the tumour from returning.

No new or unexpected safety concerns arose from this application 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.
LETROZOLE 2.5MG FILM-COATED TABLETS
PL 33410/0061

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted a Marketing Authorisation for the medicinal product Letrozole 2.5mg Film-Coated Tablets (PL 33410/0061) to APSLA Limited on 18th February 2010. This prescription only medicine is indicated for the:

- 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.

This application for Letrozole 2.5mg Film-Coated Tablets is submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product to Femara 2.5mg Film-Coated Tablets, first authorised in the UK to Novartis Pharmaceuticals UK Limited in September 1996.

The active substance, letrozole, is a reversible (Type II), nonsteroidal aromatase inhibitor. The aromatase enzyme is involved in the production of oestrogen. In postmenopausal women the aromatase enzyme converts the sex hormones androstenedione and testosterone, into oestrogen. Letrozole prevents this conversion by blocking the action of the aromatase enzyme, thus causing oestrogen levels in the body to fall.

The pharmacovigilance system as described by the applicant fulfils the requirements. It also provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring.

The Marketing Authorisation Holder has provided adequate justification for not submitting a risk management plan (RMP).
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Letrozole

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:

\[
\begin{array}{c}
\text{N} \\
\text{C} \\
\text{C} \\
\text{N} \\
\text{NC} \\
\text{CN} \\
\end{array}
\]

Letrozole

Molecular formula: \( \text{C}_{17}\text{H}_{11}\text{N}_{5} \)
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.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients in the tablet core consist of pharmaceutical excipients lactose monohydrate, sodium starch glycolate, microcrystalline cellulose, colloidal anhydrous silica, hypromellose 6 cP and magnesium stearate. The film coating consists of opadry 04F52158 yellow (hypromellose 15 cP (E464), PEG 6000, titanium dioxide (E171), iron oxide yellow (E172 (iii)), iron oxide red (E172 (II)), FD&C yellow #5 Aluminium lake (E102)).

All the ingredients comply with their relevant European Pharmacopoeia monographs.

With the exception of lactose monohydrate, none of the excipients used contain material of animal or human origin. 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 those intended for human consumption. A valid European Pharmacopoeia Certificate of Suitability for TSE for magnesium stearate contained in this product has been submitted.

**Product development**

The objective of the development programme was to produce a product that could be considered a generic medicinal product of Femara 2.5mg Film-Coated Tablets (Novartis Pharmaceuticals UK Limited, September 1996).

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished product versus the reference product Femara 2.5mg Film-Coated Tablets (Novartis Pharmaceuticals UK Limited).

**Manufacture**

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

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on three production-scale batches of finished product and the results appear satisfactory.

**Finished product specification**

The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis for all working standards used have been provided and are satisfactory.
Container-Closure System
The product is packaged in polyvinylchloride, polyvinylidene chloride, polyethylene and aluminium foil blister packs in sizes of 14 or 28 tablets.

Specifications and Certificates of Analysis for the packaging types used have been provided. All primary product packaging complies with the European Pharmacopoeia monograph.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, with the storage conditions ‘Do not store above 30°C’ and ‘Store in original package’. This is satisfactory.

ADMINISTRATIVE
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SPC)
This is pharmaceutically satisfactory.

Labelling
These are pharmaceutically satisfactory.

Patient Information Leaflet (PIL)
This is pharmaceutically satisfactory.

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 Form
This is pharmaceutically satisfactory.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.
PRE-CLINICAL ASSESSMENT

This application for Letrozole 2.5mg Film-Coated Tablets was submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product of Femara 2.5mg Film-Coated Tablets, first authorised in the UK to Novartis Pharmaceuticals UK Limited in September 1996.

No new preclinical data have been supplied with this application and none are required for applications of this type.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
To support the applications, the marketing authorisation holder has included one bioequivalence study:

A randomized, open-label, 2-sequence, 2-way crossover bioequivalence study comparing the pharmacokinetics of Letrozole 2.5mg Film-Coated Tablets (Test) versus Femara 2.5mg Tablets (Reference) in healthy post-menopausal or surgically sterile female non-smokers under fasted conditions.

Femara 2.5mg Film-Coated Tablets licensed in Spain was used as the reference product in the bioequivalence study. This is considered to be equivalent to the UK reference product, Femara 2.5mg Film-Coated Tablets.

Blood sampling was performed pre- and up to 24 hours post dose in each treatment period. There was a washout period of 28 days. 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>Letrozole:</th>
<th>AUC_{0-t} (ng/ml/h)</th>
<th>AUC_{0-\infty} (ng/ml/h)</th>
<th>C_{max} (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>1514.67</td>
<td>1618.89</td>
<td>35.75</td>
</tr>
<tr>
<td>Reference</td>
<td>1498.81</td>
<td>1599.72</td>
<td>37.28</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>96.52-103.29</td>
<td>96.44-103.41</td>
<td>96.53</td>
</tr>
</tbody>
</table>

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 has been provided.

SAFETY
No new data has been provided.

EXPERT REPORTS
The clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
These are satisfactory.

APPLICATION FORMS (MAA)
These are satisfactory.
SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
These are consistent with those for the reference products and are satisfactory.

DISCUSSION
The applicant has satisfactorily demonstrated bioequivalence between the test and reference products.

MEDICAL CONCLUSION
The bioequivalence study submitted has shown that Letrozole 2.5mg Film-Coated Tablets can be considered as a generic medicinal product to the originator product.

The grant of a Marketing Authorisation is recommended for this application.
OVERALL CONCLUSION AND RISK BENEFIT 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 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 Film-Coated Tablets (Novartis Pharmaceuticals UK Limited).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference product Femara 2.5mg Film-Coated Tablets.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with letrozole is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for this application is consistent with that previously assessed for the cross-reference product and, as such, has been judged to be satisfactory.

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 reference product Femara 2.5mg Film-Coated Tablets (Novartis Pharmaceuticals UK Limited).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference product Femara 2.5mg Film-Coated Tablets (Novartis Pharmaceuticals UK Limited).

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. Extensive clinical experience with letrozole is considered to have demonstrated the therapeutic value of the compounds. The risk:benefit is, therefore, considered to be positive.
**LETROZOLE 2.5MG FILM-COATED TABLETS**  
PL 33410/0061

**STEPS TAKEN FOR ASSESSMENT**

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 17th July 2009.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 31st July 2009.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application further information was requested regarding the quality section of the dossier on 1st October 2009.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality sections of the dossier on 3rd December 2009.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 18th February 2010.</td>
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</table>
**LETROZOLE 2.5MG FILM-COATED TABLETS**  
**PL 33410/0061**

**STEPS TAKEN AFTER ASSESSMENT**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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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.
Each tablet contains 45 mg of lactose monohydrate (see section 4.4)
For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM
Film-coated tablet
Yellow, circular, biconvex film-coated tablets plain on both sides.

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 tablet is 2.5 mg once daily. In the adjuvant setting, treatment with Letrozole tablet 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 ≥10 mL/min.), (see section 5.2).

4.3 CONTRAINDICATIONS
Known 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 tablet 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 tablet in men with breast cancer.

Letrozole tablet 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 tablet.

As Letrozole tablet 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 co-administration of Letrozole tablet 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 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 tablets 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 tablet is contraindicated during pregnancy (see section 4.3).

**Lactation**
Letrozole tablet 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 tablets 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 tablet (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 tablets and somnolence has been reported uncommonly, caution is advised when driving or using machines.

4.8 UNDESIRABLE EFFECTS
Letrozole tablet 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 tablets.

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%, not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Organ System</th>
<th>Very Common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000), not known (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td>Urinary tract infection</td>
<td></td>
<td>Tumour pain (6)</td>
<td></td>
<td>Angioedema, anaphylactic reactions</td>
</tr>
<tr>
<td>Neoplasm, benign, malignant and unspecified (including cysts and polyps)</td>
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<tr>
<td>Blood and lymphatic system disorder</td>
<td></td>
<td>Leucopenia</td>
<td></td>
<td></td>
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<tr>
<td>Immune system disorder</td>
<td></td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia, appetite increase, raised serum cholesterol</td>
<td>General oedema</td>
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<tr>
<td>Psychiatric disorders</td>
<td>Depression</td>
<td>Anxiety &lt;sup&gt;(1)&lt;/sup&gt;</td>
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<tr>
<td>Nervous system disorders</td>
<td>Headache, dizziness</td>
<td>Somnolence, insomnia, memory impairment, dysaesthesia, taste disturbance, cerebrovascular accident</td>
<td></td>
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<tr>
<td>Eye disorders</td>
<td></td>
<td>Cataract, eye irritation, blurred vision</td>
<td></td>
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<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Palpitations, tachycardia</td>
<td></td>
<td></td>
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<tr>
<td>Vascular disorder</td>
<td></td>
<td>Thrombophlebitis (3), Hypertension, ischemic cardiac events (7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td>Pulmonary embolism, arterial thrombosis, cerebrovascular infarction</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, vomiting, dyspepsia, constipation, diarrhoea</td>
<td>Abdominal pain, stomatitis, dry mouth</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hepatobiliary disorders</td>
<td>Increased hepatic enzymes</td>
<td>Hepatitis</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia, increased sweating, rash &lt;sup&gt;(4)&lt;/sup&gt;</td>
<td>Pruritus, dry skin, urticaria</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia</td>
<td>Myalgia, bone pain, osteoporosis, bone fractures</td>
<td></td>
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<td></td>
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<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td>Increased urinary frequency</td>
<td></td>
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<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td>Vaginal bleeding, vaginal discharge, vaginal dryness, breast pain</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Hot flushes</td>
<td>Fatigue &lt;sup&gt;(5)&lt;/sup&gt;, peripheral oedema</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight increase</td>
<td>Weight loss</td>
<td></td>
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</tbody>
</table>

*Including:
(1) nervousness, irritability
(2) paraesthesia, hypoaesthesia
(3) superficial and deep thrombophlebitis
(4) erythematous, maculopapular, psoriaform and vesicular rash
(5) aesthenia 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 2

<table>
<thead>
<tr>
<th>Pre-specified event</th>
<th>Letrozole N=3975 n (%)</th>
<th>Tamoxifen N=3988 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flashes/hot flushes</td>
<td>1367 (34.4)</td>
<td>1534 (38.5)</td>
</tr>
<tr>
<td>Arthralgia/arthritis</td>
<td>804 (20.2)</td>
<td>519 (13.0)</td>
</tr>
<tr>
<td>Night sweats</td>
<td>578 (14.5)</td>
<td>664 (16.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>394 (9.9)</td>
<td>424 (10.6)</td>
</tr>
<tr>
<td>Fatigue (lethargy, malaise, asthenia)</td>
<td>348 (8.8)</td>
<td>352 (8.8)</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>190 (4.8)</td>
<td>433 (10.9)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>265 (6.7)</td>
<td>236 (5.9)</td>
</tr>
<tr>
<td>Edema</td>
<td>236 (5.9)</td>
<td>231 (5.8)</td>
</tr>
<tr>
<td>Bone fractures</td>
<td>252 (6.3)</td>
<td>187 (4.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>148 (3.7)</td>
<td>139 (3.5)</td>
</tr>
<tr>
<td>Vaginal irritation</td>
<td>145 (3.6)</td>
<td>124 (3.1)</td>
</tr>
<tr>
<td>Dizziness/light-headedness</td>
<td>101 (2.5)</td>
<td>118 (3.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>110 (2.8)</td>
<td>107 (2.7)</td>
</tr>
<tr>
<td>Total serum cholesterol &gt; 1.5* ULN 1,2</td>
<td>174 (5.4)</td>
<td>36 (1.1)</td>
</tr>
<tr>
<td>Thromboembolic event</td>
<td>48 (1.2)</td>
<td>119 (3.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>62 (1.6)</td>
<td>103 (2.6)</td>
</tr>
<tr>
<td>Cerebrovascular accident/transient ischemic attack</td>
<td>48 (1.2)</td>
<td>49 (1.2)</td>
</tr>
<tr>
<td>Breast pain</td>
<td>45 (1.1)</td>
<td>50 (1.3)</td>
</tr>
<tr>
<td>Cataract</td>
<td>49 (1.2)</td>
<td>43 (1.1)</td>
</tr>
<tr>
<td>Endometrial hyperplasia or cancer 3</td>
<td>10 (0.3)</td>
<td>62 (2.0)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>33 (0.8)</td>
<td>33 (0.8)</td>
</tr>
<tr>
<td>Angina pectoris (new, or worsening or requiring surgical intervention)</td>
<td>30 (0.8)</td>
<td>30 (0.8)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>32 (0.8)</td>
<td>13 (0.3)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>20 (0.5)</td>
<td>15 (0.4)</td>
</tr>
<tr>
<td>Ovarian cyst</td>
<td>18 (0.5)</td>
<td>16 (0.4)</td>
</tr>
</tbody>
</table>

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 are appropriate.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Letrozole is a Non-steroidal aromatase inhibitor (inhibitor of oestrogen biosynthesis); antineoplastic agent.

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 are 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 3 Disease-free survival and overall survival (ITT population)**

<table>
<thead>
<tr>
<th>Event</th>
<th>Letrozole=4003</th>
<th>Tamoxifen n=4007</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free survival (DFS)</td>
<td>351</td>
<td>428</td>
<td>0.81 (0.70, 0.93)</td>
<td>0.0030</td>
</tr>
<tr>
<td>(primary (protocol definition)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>296</td>
<td>369</td>
<td>0.79 (0.68, 0.92)</td>
<td>0.0024</td>
</tr>
<tr>
<td>(ignoring second non-breast</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cancers)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distant disease-free survival</td>
<td>184</td>
<td>249</td>
<td>0.73 (0.60, 0.88)</td>
<td>0.0012</td>
</tr>
<tr>
<td>(metastases) (secondary)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral breast cancer</td>
<td>19</td>
<td>31</td>
<td>0.61 (0.35, 1.08)</td>
<td>0.0910</td>
</tr>
<tr>
<td>(invasive) (secondary)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>166</td>
<td>192</td>
<td>0.86 (0.70, 1.06)</td>
<td>0.1546</td>
</tr>
<tr>
<td>number of deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI – Confidence Interval

1Logrank test, stratified by randomisation option and adjuvant chemotherapy

**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 4 Disease-free and overall survival (Modified ITT population)**

<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>Disease-free survival (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)(^1)</td>
<td>0.00003</td>
</tr>
<tr>
<td>Distant disease-free survival</td>
<td>57</td>
<td>93</td>
<td>0.61 (0.44,0.84)(^2)</td>
<td>0.003</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>51</td>
<td>62</td>
<td>0.82 (0.56,1.19)(^1)</td>
<td>0.291</td>
</tr>
<tr>
<td>Contralateral breast cancer (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)(^3)</td>
<td>0.120</td>
</tr>
<tr>
<td>- invasive</td>
<td>15</td>
<td>25</td>
<td>0.60 (0.31,1.14)(^3)</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 C_{max}, 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**
- Lactose monohydrate
- Sodium starch glycolate
- Microcrystalline cellulose
- Hylomellose 6 cP
- Colloidal anhydrous silica
- Magnesium stearate (E572)

**Film coat**
Opadry 04F52158 Yellow:
Hylomellose 15 cP, (E464)
PEG 6000  
Titanium dioxide, (E171)  
Iron oxide yellow, E172 (iii)  
Iron oxide red, E172 (ii)  
FD&C yellow #5 Aluminium lake, (E102)

6.2 INCOMPATIBILITIES  
None known.

6.3 SHELF LIFE  
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE  
Do not store above 30°C. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER  
PVC/PE/PVDC Aluminium blister packs of 14 or 28 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL  
No specific instructions for use/handling.

7 MARKETING AUTHORISATION HOLDER  
APSLA Limited,  
Bayview House,  
49 North Strand Road,  
Dublin 3,  
Ireland.

8 MARKETING AUTHORISATION NUMBER(S)  
PL 33410/0061

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION  
18/02/2010

10 DATE OF REVISION OF THE TEXT  
18/02/2010
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 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 Tablets are and what they are used for
2. Before you take Letrozole Tablets
3. How to take Letrozole Tablets
4. Possible side effects
5. How to store Letrozole Tablets
6. Further information

1. WHAT LETROZOLE TABLETS ARE AND WHAT THEY ARE USED FOR

Letrozole, the active ingredient in Letrozole tablets, is one of a group of medicines called aromatase inhibitors. These block the production of oestrogens.

Letrozole tablets are used to treat breast cancer in post-menopausal women. They can be used either before surgery to reduce the size of the tumour, or after surgery to help prevent the tumour from returning.

They can also be used in patients with advanced breast cancer to help stop the tumour spreading to other parts of the body.

2. BEFORE YOU TAKE LETROZOLE TABLETS

Do not take Letrozole tablets
- if you think you may be allergic to letrozole or to any of the other ingredients of Letrozole Tablets (These are listed in Section 6.)
- if you have not yet gone through menopause.
- if you are pregnant or if there is a possibility that you might be pregnant.
- if you are breast-feeding.
- If you have a serious liver disease.

Take special care with Letrozole Tablets
- if you suffer from any serious kidney disease.
- if you have an inherited intolerance to some sugars such as lactose. The tablets contain a small amount of lactose
- if you have a history of osteoporosis (thinning or wasting of bones) or bone fractures. Your doctor may want to measure your bone density before and during your treatment. Drugs like Letrozole Tablets reduce the levels of female hormones. This can lead to a loss of minerals in bones and cause osteoporosis (decrease in bone density and strength).
Taking other medicines
Please tell your doctor if you are taking or have recently taken any other medicines including medicines obtained without a prescription.

Children and adolescents (below 18 years)
Letrozole is not to be used in children or adolescents.

Older people (age 65 years and over)
Letrozole tablet can be used by people aged 65 years and over at the same dose as for other adults.

Taking Letrozole tablets with food and drink
Taking food and drink has no influence on your treatment with Letrozole tablets.

Pregnancy and breast-feeding
Letrozole tablets are not recommended during pregnancy and breast-feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machine
Do not drive or work with machinery, if you feel dizzy, tired or drowsy when you start to take Letrozole Tablets.

Important information about some of the ingredients of Letrozole Tablets
Letrozole Tablets contain lactose. 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 TABLETS

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

The usual dose of Letrozole Tablets is 1 tablet once a day. You will probably continue to take Letrozole tablets for a number of years.

If you take more Letrozole Tablets than you should
If you accidentally take too many Letrozole Tablets, than you have been told to take, tell your doctor at once or contact your nearest hospital casualty department. Take your medicine with you.

If you forget to take Letrozole Tablets
Do not take a double dose to make up for a forgotten dose, take it as soon as you remember. Then take your next dose as usual.
Do not stop taking your tablets, even if you are feeling well, unless your doctor tells you. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, letrozole tablets can cause side effects, although not everybody gets them.
Most of the side effects are mild or moderate and will generally disappear after a few days to few weeks of treatment.
Some side effects can be serious
Severe allergic reactions, angina, heart attack, thrombosis, pulmonary embolism or stroke have occasionally been reported as side effects.

Stop taking the tablets and tell your doctor or go to the emergency department at your nearest hospital IMMEDIATELY if you get any of the following symptoms:
• Heavy or tight chest or pain in the chest, spreading to your arms or shoulders, neck, teeth or jaw, abdomen or back
• Coughing blood
• Unusual pains or swelling of your arms or legs

XXXXX
• Sudden shortness of breath, difficulty in speaking or breathing
• Fainting
• Numbness or weakness in your arm or leg or any part of your body
• Loss of co-ordination
• Vision changes
• Sudden severe headache
• Severe rash and itching, swollen throat, face, eyelids or lips, difficulty breathing

The side effects listed below have also been reported:

The most common side effects experienced by more than 10% of people are:
• Hot flushes
• Pains in the joints (arthralgia)

Up to 1 in 10 people have experienced:
• Loss of appetite or increased appetite
• Feeling or being sick, indigestion, constipation, diarrhoea
• Weight gain
• Raised cholesterol levels
• Depression
• Headache
• Dizziness
• Hair loss
• Increased sweating
• Skin rash
• Muscle pain
• Bone problems (pain, bone thinning (osteoporosis), fractures)
• Feeling tired
• Swelling in the legs or feet due to fluid retention

Up to 1 in 100 people have experienced:
• Urinary tract infections, urinating more often
• Pain in the breast including in the tumour or in the stomach
• General swelling due to fluid retention
• Decreased white blood cells which can lead to infections (leucopenia)
• Mental problems (anxiety, nervousness, irritability, loss of memory)
• Sleep problems (sleepiness or difficulty in sleeping)
• Changes in sensation, including touch sensation (pins and needles), taste changes
• Eye problems such as cataract (loss of transparency of the lens of the eye), eye irritation, blurred vision, dry eyes
• Heart problems such as palpitations, fast heart beat (tachycardia) irregular heart beat (arrhythmia), angina and heart attacks
• Inflamed blood vessels
• Hypertension (raised blood pressure)
• Breathlessness
• Dry mouth or mouth ulcers
• Liver problems
• Dry or itchy skin or raised wheals
• Arthritis (inflammation of the joints)
• Vaginal bleeding, vaginal discharge, vaginal dryness
• Fever
• Thirst
• Weight loss
• Cough
Up to 1 in 1,000 people have experienced:
- Thrombosis (clotting in the blood vessels e.g. legs)
- Pulmonary embolism (a blood clot in the lungs)

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 TABLETS

Store in the original package.
Keep all medicines out of the reach and sight of children.
Do not take Letrozole tablets after the expiry date which is stated on the carton after “EXP”. The expiry date refers to the last day of that month.
If your doctor tells you to stop taking Letrozole tablets, please take any unused tablets back to your pharmacist to be destroyed. Only keep the tablets if the doctor tells you to.

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 protect the environment.

6. FURTHER INFORMATION

What Letrozole tablet contains
- Each film-coated tablet contains 2.5 mg letrozole
- The other ingredients are lactose monohydrate, sodium starch glycollate, microcrystalline cellulose, hypromellose 6 cP, colloidal anhydrous silica, magnesium stearate.
- The film coat contains hypromellose 15 cP, macrogol 6000, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172) and tartrazine (E102).

What Letrozole tablet looks like and contents of the pack
Letrozole 2.5 mg film-coated tablets are yellow, circular, biconvex film-coated tablets with LTZ on one side and plain on the other side.
Letrozole 2.5 mg film-coated tablets are available in blister packs of 14 and 28 tablets.

Marketing Authorisation Holder
APSLA Limited, Bayview House, 49 North Strand Road, Dublin 3, Ireland.

Manufacturer:
Recipharm Limited, Vale of Bardsley, Ashton-Under-Lyne, Lancashire, OL7 9RR, United Kingdom.

Marketed and Distributed By:
APC Pharmaceuticals & Chemicals (Europe) Limited, Suite 505, Park House, 111 Uxbridge Road, Ealing, London W5 5LB

This leaflet was approved in {MM/YYYY}
Letrozole 2.5 mg film-coated tablets
Letrozole
28 film-coated tablets

Each film-coated tablet contains 2.5 mg of Letrozole

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UKPAR Letrozole 2.5mg Film-Coated Tablets

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