Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Letrozole 2.5 mg Film-Coated Tablets

letrozole

PL 55863/0013

NOVUMGEN LIMITED

LAY SUMMARY

Letrozole 2.5 mg Film-Coated Tablets
letrozole

This is a summary of the Public Assessment Report (PAR) for Letrozole 2.5 mg Film-Coated Tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Letrozole 2.5 mg Film-Coated Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Letrozole 2.5 mg Film-Coated Tablets and what is it used for?
This product is a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Femara 2.5 mg film-coated tablets.

Letrozole is used to treat breast cancer in women who have gone through menopause i.e cessation of periods. It is used to prevent cancer from happening again. It can be used as first treatment before breast cancer surgery in case immediate surgery is not suitable or it can be used as first treatment after breast cancer surgery or following five years treatment with tamoxifen. Letrozole is also used to prevent breast tumour spreading to other parts of the body in patients with advanced breast cancer.

How do Letrozole 2.5 mg Film-Coated Tablets work?
Letrozole 2.5 mg Film-Coated Tablets contains an active substance called letrozole. It belongs to a group of medicines called aromatase inhibitors. It is a hormonal (or "endocrine") breast cancer treatment.

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

How are Letrozole 2.5 mg Film-Coated Tablets used?
The pharmaceutical form of this medicine is film-coated tablets and the route of administration is oral (by mouth). The tablet can be taken with or without food and should be swallowed whole with a glass of water or another liquid. Taking Letrozole 2.5 mg Film-Coated Tablets at the same time each day will help patients remember when to take their tablet.

The usual dose is one tablet to be taken once a day. Older people such as those aged 65 years and over can use this medicine at the same dose as for other adults. Children and adolescents (below 18 years) should not use this medicine.

Patients should continue taking Letrozole 2.5 mg Film-Coated Tablets every day for as long as their doctor tells them to do so. This may be for months or even years.

This medicine should only be taken under strict medical supervision. The patient's doctor

will regularly monitor their condition to check whether the treatment is having the right effect. Letrozole may cause thinning or wasting of patient's bones (osteoporosis) due to the reduction of oestrogens in the body, and the patient's doctor may decide to measure their bone density (a way of monitoring for osteoporosis) before, during and after treatment.

For further information on how Letrozole 2.5 mg Film-Coated Tablets is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Letrozole 2.5 mg Film-Coated Tablets have been shown in studies?
Because Letrozole 2.5 mg Film-Coated Tablets is a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Letrozole 2.5 mg Film-Coated Tablets?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Letrozole 2.5 mg Film-Coated Tablets is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are considered to be the same as the reference medicine.

Why were Letrozole 2.5 mg Film-Coated Tablets approved?
It was concluded that, Letrozole 2.5 mg Film-Coated Tablets has been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Letrozole 2.5 mg Film-Coated Tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Letrozole 2.5 mg Film-Coated Tablets. The RMP details the important risks of Letrozole 2.5 mg Film-Coated Tablets, how these risks can be minimised, any uncertainties about Letrozole 2.5 mg Film-Coated Tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Letrozole 2.5 mg Film-Coated Tablets:

Important identified risks	• Hypersensitivity to the active substance or to any of the excipients • Lipid metabolism (hypercholesterolemia) • Bone Health (osteoporosis/osteopenia; fractures) • Ischemic heart disease • Cerebrovascular accidents • Congenital malformations • Co-administration of letrozole with tamoxifen
Important potential risks	• None
Important missing information	• None

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Letrozole 2.5 mg Film-Coated Tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Letrozole 2.5 mg Film-Coated Tablets
A marketing authorisation for Letrozole 2.5 mg Film-Coated Tablets was granted in the United Kingdom (UK) on 7 May 2024.

The full PAR for Letrozole 2.5 mg Film-Coated Tablets follows this summary.

This summary was last updated in September 2024.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Letrozole 2.5 mg Film-Coated Tablets (PL 55863/0013) could be approved.

The product is approved for the following indications:

- Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.
- Extended adjuvant treatment of hormone-dependent invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy for 5 years.
- First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer.
- Advanced breast cancer after relapse or disease progression, in women with natural or artificially induced postmenopausal endocrine status, who have previously been treated with anti-oestrogens.
- Neo-adjuvant treatment of postmenopausal women with hormone receptor positive, HER-2 negative breast cancer where chemotherapy is not suitable and immediate surgery not indicated.

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

Letrozole is a non-steroidal aromatase inhibitor. It inhibits the aromatase enzyme by competitively binding to the haem of the aromatase cytochrome P450, resulting in a reduction of oestrogen biosynthesis in all tissues where present. In healthy postmenopausal women, single doses of 0.1 mg, 0.5 mg, 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 hours.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Femara 2.5 mg film-coated tablets that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation for Letrozole 2.5 mg Film-Coated Tablets was granted in the United Kingdom (UK) on 7 May 2024.

II QUALITY ASPECTS

II.1 Introduction

This product consists of 2.5 mg letrozole.

In addition to letrozole, this product also contain the excipients:

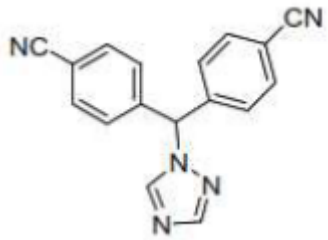
- Tablet core: lactose monohydrate, cellulose microcrystalline (E 460), sodium starch glycolate, starch pregelatinised, silica colloidal anhydrous (E 551), purified water and magnesium stearate (E 572).
- Film coating: Opadry yellow (03F420010), hypromellose (E 464), talc (E 553b), macrogol (E 1521), iron oxide yellow (E 172) and titanium dioxide (E 171).

The finished product is packaged in PVC/PVDC/aluminium blisters in packs of 10, 14, 28, 30, 60, 90 or 100 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: letrozole
Chemical Name: 4, 4'-(1H-1,2,4-Triazol-1-yl) methylene] dibenzo nitrile
Molecular Formula: $C_{17}H_{11}N_5$



Chemical Structure:
Molecular Weight: 285.31
Appearance: white or yellowish crystalline powder
Solubility: soluble in acetonitrile, acetone, and tetrahydrofuran; slightly soluble in ethanol; sparingly soluble in methanol and ethyl acetate; insoluble in n-hexane and water

Letrozole is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution and impurity profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

This product does not contain or consist of genetically modified organisms (GMO).

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

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

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 36 months (3 years), with no special storage conditions is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of letrozole are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology
No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of letrozole is well-known. With the exception of data from the single bioequivalence study 008-20, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics
In support of the application, the applicant submitted the following:

Bioequivalence study 008-20 (single oral dose; fasting)
This study was a randomised, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, two way crossover, truncated, oral bioequivalence study comparing the test product Letrozole 2 mg film-coated tablets versus the reference product Femara (letrozole) 2.5 mg film-coated tablets in healthy adult human post-menopausal female subjects under fasted conditions.

After at least a 10 hour fast overnight, subjects were administered a single dose of either the test or the reference product. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of at least 28 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Parameter	N	GLSMR	GLSMT	T/R Ratio	90% CI Lower	90% CI Upper	Power	ISCV	BE
C_{max}	36	33.596	34.233	101.90%	95.02%	109.26%	99.96%	17.65%	YES
AUC_{0-72}	36	1021.425	1060.764	103.85%	101.17%	106.60%	100.00%	6.56%	YES

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted for this application and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with this application and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation was recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. 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.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved UK version of the SmPC and PIL for this product are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**