Letrozole 2.5mg film-coated tablets

PL 40378/0145

UKPAR

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The Medicines and Healthcare products Regulatory Agency (MHRA) granted APTIL Pharma Limited a Marketing Authorisation (licence) for the medicinal product Letrozole 2.5mg film-coated tablets (PL 40378/0145) on 03 October 2012. 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 amount of oestrogen by blocking an enzyme (aromatase) involved in the production of oestrogens. As a consequence, tumour cells slow or stop growing and/or spreading to other parts of the body.

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.

This application is for a product considered to be identical to the previously granted licence for Letrozole 2.5mg film-coated tablets (PL 33410/0061), authorised to APSLA Limited on 15 February 2010.

No new or unexpected safety concerns arose from this application. It was judged that the benefits of Letrozole 2.5mg film-coated tablets outweigh the risks; hence a Marketing Authorisation was granted.
Letrozole 2.5mg film-coated tablets

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted APTIL Pharma Limited a Marketing Authorisation for the medicinal product Letrozole 2.5mg film-coated tablets (PL 40378/0145) on 03 October 2012. The product is a prescription-only medicine.

This is a simple, abridged, ‘informed consent’ application submitted according to Article 10(c) of EC Directive 2001/83 (as amended), cross-referencing the Marketing Authorisation for Letrozole 2.5mg film-coated tablets (PL 33410/0061), authorised to APSLA Limited on 15 February 2010.

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 and oestradiol. The suppression of oestrogen biosynthesis in peripheral tissues and the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme. Letrozole is a non-steroidal aromatase inhibitor (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 (CLm= 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.

The MHRA considers that the pharmacovigilance system described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence
that the MAH has the services of a Qualified Person (QP) 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 MAH has provided adequate justification for not submitting a Risk Management Plan. As the application is for a product that is identical to an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well-established.

No new data were submitted nor required for this simple application, as the data package is identical to that of the previously granted cross-reference product. A Public Assessment Report (PAR) is available for the cross-reference product, Letrozole 2.5mg film-coated tablets (PL 33410/0061).
PHARMACEUTICAL ASSESSMENT

LICENCE NUMBER: PL 40378/0145
PROPRIETARY NAME: Letrozole 2.5mg film-coated tablets
ACTIVE INGREDIENTS: Letrozole
COMPANY NAME: APTIL Pharma Limited
E.C. ARTICLE: Article 10(c) of Directive 2001/83/EC (as amended)
LEGAL STATUS: POM

1. INTRODUCTION

This is a simple abridged application, submitted under Article 10(c) of Directive 2001/83/EC (as amended) for Letrozole 2.5mg film-coated tablets. The proposed Marketing Authorisation Holder (MAH) is APTIL Pharma Limited.

The reference product is Letrozole 2.5mg film-coated tablets (PL 33410/0061), authorised to APSLA Limited on 15 February 2010. The proposed and reference products are identical.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The approved name of the product is Letrozole 2.5mg film-coated tablets. The product has been named in line with current requirements and the product name is acceptable.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

Each Letrozole 2.5mg film-coated tablet contains 2.5mg of the active ingredient, letrozole. The tablets are licensed for marketing in polyvinylchloride (PVC)-polyethylene (PE)-polyvinylidene chloride (PVdC)-aluminium foil blister strips which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 14 or 28.

The container closure system is identical to that stated for the reference product.

The approved shelf-life (2 years) and storage instructions (‘Store in the original package’) are identical to the details registered for the reference product.

2.3 Legal status

POM - The product is available subject to a medical prescription.

2.4 Marketing Authorisation Holder / Contact Persons / Company

The proposed Marketing Authorisation Holder is APTIL Pharma Limited, 9th Floor, CP House, 97 – 107 Uxbridge Road, Ealing, London W5 5TL.

The Qualified Person (QP) responsible for pharmacovigilance was stated and their CV included.
2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed composition is consistent with that registered for the cross-reference product.

2.7 Manufacturing process
The proposed manufacturing process is consistent with that registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product / shelf-life specification
The proposed finished product specification is consistent with that registered for the cross-reference product.

2.9 Drug substance specification
The proposed drug substance specification is consistent with that registered for the cross-reference product.

2.10 TSE Compliance
The only excipient used that contains material of animal or human origin is magnesium stearate. A satisfactory TSE declaration has been provided for magnesium stearate, stating that it meets the criteria described in the current version of the European Pharmacopoeia monograph ‘Products with risk of transmitting agents of animal spongiform encephalopathies’. None of the excipients are sourced from genetically modified organisms.

3. EXPERT REPORT
A satisfactory quality overall summary has been prepared by an appropriately qualified expert. The CV of the expert was provided.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The appearance of the product (yellow, circular, biconvex film-coated tablets plain on both sides) is identical to that of the cross-reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The proposed SmPC is consistent with that registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET (PIL)/LABELLING
The proposed PIL is satisfactory and in line with the SmPC. It has been prepared according to the Quality Review of Documents (QRD) template and is consistent with the leaflet registered for the cross-reference product.
PIL user-testing has been accepted based on bridging to the successful user-testing of the PIL for the reference product, Letrozole 2.5mg film-coated tablets (PL 33410/0061, APLS Limited). The text, content and layout of the proposed PIL are essentially identical to the approved PIL for the reference product. The bridging is accepted.

Mock-ups of the labelling have been provided and are satisfactory. The approved artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements.

7. CONCLUSIONS

The grounds for this application were considered adequate and a Marketing Authorisation was therefore granted.
NON-CLINICAL ASSESSMENT

This is a simple, abridged, ‘informed consent’ application made under Article 10(c) of EC Directive 2001/83 (as amended).

No new non-clinical data have been supplied with this application and none are required for an application of this type. A non-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the non-clinical expert has been supplied.

There is no reason to conclude that marketing of this product will change the overall use pattern of the existing market. The availability of this medicinal product, which is identical to the cited reference product, will not lead to any increase in environmental exposure concentrations of the active ingredient. An Environmental Risk Assessment (ERA) is not considered necessary.
CLINICAL ASSESSMENT

This is a simple, abridged, ‘informed consent’ application made under Article 10(c) of EC Directive 2001/83 (as amended), cross-referring to the Marketing Authorisation for Letrozole 2.5mg film-coated tablets (PL 33410/0061, APSLA Limited).

No new clinical data have been supplied with the application and none are required for applications of this type. A clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the clinical expert has been supplied.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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

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

CLINICAL
This application is considered identical to the previously granted licence for Letrozole 2.5mg film-coated tablets (PL 33410/0061, APSLA Limited).

No new data are provided and no new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE
The approved SmPC, PIL and labelling are satisfactory and consistent with those registered for the cross-reference product.

PIL user-testing has been accepted based on bridging to the successful user-testing of the ‘parent’ PIL for Letrozole 2.5mg film-coated tablets (PL 33410/0061, APSLA Limited). The results show that the leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. The benefit: risk ratio is considered to be positive.
Letrozole 2.5mg film-coated tablets

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STEPS TAKEN FOR ASSESSMENT

1  The MHRA received the Marketing Authorisation application on 20 July 2012.

2  Following standard checks and communication with the applicant the MHRA considered the application valid on 26 July 2012.

3  The application was approved on 03 October 2012.
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STEPS TAKEN AFTER AUTHORISATION

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
LABELLING
Braille text reads as follows:

le tro zo le
# 2 . 5 m g
fi lm - co ated
tablets

# denotes unique number symbol