Public Assessment Report

Tamoxifen 20 mg Tablets
(tamoxifen citrate)

UK Licence No: PL 20395/0010

Relonchem Limited
LAY SUMMARY
Tamoxifen 20 mg Tablets
(tamoxifen citrate)

This is a summary of the public assessment report (PAR) for Tamoxifen 20 mg Tablets (PL 20395/0010). It explains how Tamoxifen 20 mg Tablets were assessed and their authorisation recommended as well as their conditions of use. It is not intended to provide practical advice on how to use Tamoxifen 20 mg Tablets.

For practical information about using Tamoxifen 20 mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Tamoxifen 20 mg Tablets and what are they used for?
Tamoxifen 20 mg Tablets are a ‘generic medicine’. This means that Tamoxifen 20 mg Tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Nolvadex D (AstraZeneca UK Ltd; PL 17901/0034).

Tamoxifen is used to treat:
- breast cancer
- infertility caused by failure to produce and release eggs (ovulate) properly
- reduce the risk of breast cancer occurring in those women who have an increased likelihood of developing breast cancer

How are Tamoxifen 20 mg Tablets used?
Tamoxifen 20 mg Tablets are taken orally. The whole tablet must be swallowed with a glass of water.

For breast cancer the recommended dose is one 20 mg tablet daily.

The dose for infertility depends on the patient’s periods (menstrual cycle).

The recommended dose in patients with regular periods is one 20 mg tablet daily on the 2nd, 3rd, 4th and 5th days of the period.

If this does not work a doctor may suggest that the patient take higher dose of Tamoxifen tablets during the next period. If this happens the recommended dose is 40 mg or 80 mg daily on the 2nd, 3rd, 4th and 5th days of their period.

Patients who do not have regular periods can start taking the tablets on any day of the month.

The recommended dose for reducing the risk of breast cancer is 20 mg daily for 5 years. A healthcare professional will calculate the risk of breast cancer occurring using information about the patient, the medical history and any family history of breast cancer.

This medicine can only be obtained with a prescription.

For further information on how Tamoxifen 20 mg Tablets are used, please see the Summary of Product Characteristics or the package leaflet available on the MHRA website.

How do Tamoxifen 20 mg Tablets work?
The medicine contains the active ingredient tamoxifen citrate, which belongs to a group of medicines called anti-oestrogens. Oestrogen is a natural substance in the body known as a 'sex hormone'. Some breast cancers need oestrogen to grow. Tamoxifen works by blocking the effects of oestrogen.

**How have Tamoxifen 20 mg Tablets been studied?**

Because Tamoxifen 20 mg Tablets are a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Nolvadex D (Nolvadex 20 mg Tablets). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the benefits and risks of Tamoxifen 20 mg Tablets?**

Because Tamoxifen 20 mg Tablets are a generic medicine that is bioequivalent to the reference medicine, their benefits and risks are taken as being the same as the reference medicine.

**Why are Tamoxifen 20 mg Tablets approved?**

It was concluded that, in accordance with EU requirements, Tamoxifen 20 mg Tablets have been shown to have comparable quality and to be bioequivalent to Nolvadex D. Therefore, the view was that, as for Nolvadex D, the benefit outweighs the identified risk.

**What measures are being taken to ensure the safe and effective use of Tamoxifen 20 mg Tablets?**

Safety information has been included in the summary of product characteristics and the package leaflet for Tamoxifen 20 mg Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Tamoxifen 20 mg Tablets**

A Marketing Authorisation was granted on 30 September 2009.

The indication, primary prevention of breast cancer, was added by variation on 24 September 2018.

The full PAR for Tamoxifen 20 mg Tablets follows this summary.

This summary was last updated in October 2018.
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I INTRODUCTION
The MHRA granted Relonchem Limited a Marketing Authorisation (licence) for the medicinal product Tamoxifen 20 mg Tablets (PL 20395/0010) on 30 September 2009. This product is a prescription only medicine (POM), indicated for the treatment of breast cancer and anovulatory infertility.

This is an abridged application made under Article 10.1 of EC Directive 2001/83, as amended. The applicant claims that the proposed product is a generic version of Nolvadex 20 (PL 17901/0034) licensed to AstraZeneca UK Ltd on 11 June 2000 following a change of ownership. The original brandleader marketing authorisation (PL 00029/0155) was granted in 1982, hence, has been marketed in the EEA for more than 10 years.

Tamoxifen is an oestrogen-receptor antagonist. It is used in the adjuvant endocrine therapy of early breast cancer and also to stimulate ovulation in women with anovulatory infertility.

The basis of this application depends on the bioequivalence study comparing the applicant’s product with the corresponding strength of the brandleader, taken from the UK market.

No new non-clinical studies were conducted, which is acceptable given that the application is a generic application based on an originator product that has been licensed for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is a generic application based on an originator product that has been licensed for over 10 years.

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

The indication, primary prevention of breast cancer, was added by variation on 24 September 2018.
II  QUALITY ASPECTS
II.1  INTRODUCTION
The product is presented as a tablet. Each tablet contains 30.4 mg tamoxifen citrate (equivalent to 20mg tamoxifen).

Other ingredients consist of the pharmaceutical excipients, calcium hydrogen phosphate, microcrystalline cellulose, sodium starch glycolate, providone, magnesium stearate and colloidal anhydrous silica.

All excipients are controlled in line with the relevant Ph. Eur. monograph. Appropriate justification for the inclusion of each excipient has been provided. Satisfactory certificates of analysis have been provided for all excipients.

The applicant has provided satisfactory certificates stating that neither the excipients nor the active substance contains substances of human or animal origin.

There were no novel excipients used and no overages.

The finished product is packed in blister strips (aluminium foil / polyvinylchloride (PVC) film dark green coloured) that are then put in a carton which will contain 30 tablets.

Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food. Stability results are considered acceptable to demonstrate the compatibility of the product with the proposed packaging.

II.2  DRUG SUBSTANCE
Tamoxifen citrate
INN: Tamoxifen citrate
Chemical name(s): (Z)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]ethylamine citrate

Structure:

Molecular formula: C_{26}H_{29}NO, C_{6}H_{8}O_{7}
Molecular weight: 563.6 g/mol
Physical form: A white or almost white powder. It is slightly soluble in water and acetone but soluble in methanol.

An appropriate specification in line with the Ph Eur monograph has been provided.

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 certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Full specifications are provided for the packaging used to store the tamoxifen, these are satisfactory.

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

II.3. Medicinal Product

Pharmaceutical development
The objective of the pharmaceutical development programme was to produce safe, tolerable tablet that could be considered a generic medicinal product of the originator product Nolvadex D (AstraZeneca UK Ltd)

Results of comparative dissolution tests of the applicant’s product versus the UK brand leader product Nolvadex have been provided. The proposed product was shown to have a comparative dissolution profile to the UK brand leader product.

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on product batches and the results are satisfactory.

Finished Product Specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. The 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 have been provided for any working standards used.

Stability of the Product
Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 3 years, with storage conditions “Do not store above 25 °C” and “Store in the original package”.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of tamoxifen citrate are well-known, no further non-clinical studies are required, and none have been provided.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ non-clinical pharmacology, pharmacokinetics and toxicology.
Tamoxifen 20 mg Tablets

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
A suitable justification has been provided for non-submission of an environmental risk assessment. As this product is intended for generic substitution with products currently marketed, the environmental burden is not expected to increase. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

III.6 Discussion on the non-clinical aspects
The grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS
IV.1 Introduction
INDICATIONS
Tamoxifen 20mg Tablets are indicated for:
1. The treatment of breast cancer.
2. The treatment of anovulatory infertility.
3. Primary prevention of breast cancer

The indication, primary prevention of breast cancer, was added by variation on 24 September 2018.

POSOLOGY AND METHOD OF ADMINISTRATION
Route of administration: ORAL

1. Breast cancer
   Adults
   The recommended daily dose of tamoxifen is normally 20mg. No additional benefit, in terms of delayed recurrence or improved survival in patients, has been demonstrated with higher doses. Substantive evidence supporting the use of treatment with 30-40 mg per day is not available, although these doses have been used in some patients with advanced disease.

   Elderly
   Similar dosing regimens of Tamoxifen 20mg Tablets have been used in elderly patients with breast cancer and in some of these patients it has been used as sole therapy.

2. Anovulatory Infertility
   Before commencing any course of treatment, whether initial or subsequent, the possibility of pregnancy must be excluded. In women who are menstruating regularly, but with anovular cycles, the initial course of treatment consists of 20mg daily in single or divided doses, given on the second, third, fourth and fifth days of menstrual cycle. If unsatisfactory basal temperature records or poor pre-ovulatory cervical mucus indicate that this initial course of treatment has been unsuccessful, further courses may be given during subsequent menstrual periods, increasing the dosage to 40mg and then to 80 mg daily in single or divided doses.
In women who are not menstruating regularly, the initial course may begin on any day. If no signs of ovulation are demonstrable, then a subsequent course of treatment may start 45 days later, with dosage increase as above. If a patient responds with menstruation, then the next course of treatment is commenced on the second day of the cycle.

3. **Primary prevention of breast cancer**

Tamoxifen 20mg Tablets treatment for the primary prevention of breast cancer should only be initiated by a medical practitioner experienced in prescribing for this indication, and as part of shared care pathway arrangement, with appropriate patient identification management and follow up.

The recommended dose is 20 mg daily for 5 years for those women at moderate or high risk. There are insufficient data to support a higher dose or longer period of use.

Before commencing treatment, an assessment of the potential benefits and risks is essential, including calculating a patient’s risk of developing breast cancer according to local guidelines and risk assessment tools. Validated algorithms are available that calculate breast cancer risk based on features such as age, family history, genetic factors, reproductive factors and history of breast disease.

The use of Tamoxifen tablets should be as part of a program including regular breast surveillance tailored to the individual woman, taking into account her risk of breast cancer.

Paediatric population

The use of Tamoxifen 20mg Tablets is not recommended in children, as safety and efficacy have not been established (see sections 5.1 and 5.2).

No toxicology data has been submitted or is required for this application. A toxicological Expert report has been submitted.

This report states that Tamoxifen is well tolerated overall but that over the past 5 years, a number of case reports and clinical trials have associated tamoxifen therapy with an increased incidence of endometrial carcinoma. It concludes that the potential carcinogenic effect of tamoxifen in humans has to be considered and WHO has formally assessed tamoxifen as a carcinogenic drug.

There is no strong association with the duration of therapy and the incidence of endometrial carcinoma, and tamoxifen is not associated with high-grade, poor prognosis disease. The WHO Expert Committee has included again tamoxifen in the current list of ‘Model List of Essential Drugs’. Therefore, several authors conclude that the benefits of tamoxifen in lives saved exceed the incidence of endometrial carcinoma.

However, because of the fact that the optimal duration to adjuvant therapy is not known and furthermore, drug resistance with changes of receptor status as well as stimulation of tumour growth may occur, the long-term tamoxifen treatment should be limited to 5 years.

**IV.2 Pharmacokinetics**

A bio-equivalence study has been submitted comparing Tamoxifen 20 mg Tablets with the equivalent dose of Nolvadex D.

**Bio-equivalence Study**
This study investigated the pharmacokinetics, distribution and the relative bio-availability of tamoxifen in healthy volunteers. The study was an open label, fixed dose study with five different study groups.

Study Groups were given either 20 mg of Nolvadex D or 20 mg Tamoxifen Tablets

There were 18 patients in each group which were studied in the fasting state.

The pharmacokinetics of Tamoxifen 20 mg Tablets and N-desmethyltamoxifen was evaluated and comparisons made between Study Groups I and II and between Study groups III and IV.

Results
The study report includes information on the 20 mg formulations only.

Tamoxifen 20 mg Tablets
There were no statistical differences between the treatment groups. Thus, the two groups can be considered identical based on demographic criteria for age, weight, height and body surface area.

The statistical calculations for the bio-availability of tamoxifen and N-desmethyltamoxifen from the reference Nolvadex 20 mg and the applicant' Tamoxifen 20 mg Tablets are shown in Tables 1 and 2, below:

Table 1:
Mean Pharmacokinetic Parameters of Tamoxifen after a Single Oral Dose of 20mg Tamoxifen (Nolvadex® 20 or Tamoxifen 20mg Tablets)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PHARMACOKINETIC</th>
<th>NOLVADEX® 20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>mean</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>18</td>
<td>31.0</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>18</td>
<td>5.28</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-1&lt;/sub&gt; (ng·h/ml)</td>
<td>18</td>
<td>2070</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-oo&lt;/sub&gt; (ng·h/ml)</td>
<td>18</td>
<td>2250</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>18</td>
<td>126</td>
</tr>
<tr>
<td>Parameter</td>
<td>n</td>
<td>mean</td>
</tr>
<tr>
<td>--------------------</td>
<td>----</td>
<td>------</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>18</td>
<td>30.7</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>18</td>
<td>5.31</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-1&lt;/sub&gt; (ng·h/ml)</td>
<td>18</td>
<td>2030</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng·h/ml)</td>
<td>18</td>
<td>2240</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>18</td>
<td>138</td>
</tr>
</tbody>
</table>

**Table 2:**
Statistical Results of Testing Treatment with Tamoxifen 20mg Tablets against Treatment with Nolvadex® 20 Using Mean Square Error Term From two Treatment ANOVA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diff (%)</th>
<th>Stat</th>
<th>Power</th>
<th>90% sym Cl</th>
<th>90% shortest cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>0.8</td>
<td>n.s.d.</td>
<td>0.916</td>
<td>8.40</td>
<td>89.4 to 0.91</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>0.6</td>
<td>n.s.d.</td>
<td>0.979</td>
<td>6.90</td>
<td>92.4 to 108.8</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-1&lt;/sub&gt; (ng·h/ml)</td>
<td>2.1</td>
<td>n.s.d.</td>
<td>0.919</td>
<td>9.70</td>
<td>88.1 to 107.7</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng·h/ml)</td>
<td>0.8</td>
<td>n.s.d.</td>
<td>0.906</td>
<td>8.50</td>
<td>89.2 to 109.2</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>9.8</td>
<td>n.s.d.</td>
<td>0.928</td>
<td>17.2</td>
<td>100.2 to 119.4</td>
</tr>
</tbody>
</table>
### Results for n-desmethyltamoxifen

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diff (%)</th>
<th>Stat</th>
<th>Power</th>
<th>90% sym Cl (%)</th>
<th>90% shortest Cl (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>c&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>12.7</td>
<td>n.s.d.</td>
<td>0.433</td>
<td>26.9</td>
<td>69.0 to 105.7</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>19.5</td>
<td>n.s.d.</td>
<td>0.236</td>
<td>40.0</td>
<td>54.0 to 107.1</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-1&lt;/sub&gt; (ng·h/ml)</td>
<td>7.7</td>
<td>n.s.d.</td>
<td>0.865</td>
<td>16.0</td>
<td>97.0 to 118.5</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-oo&lt;/sub&gt; (ng·h/ml)</td>
<td>6.1</td>
<td>n.s.d.</td>
<td>0.719</td>
<td>16.1</td>
<td>93.2 to 119.1</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>8.5</td>
<td>n.s.d.</td>
<td>0.480</td>
<td>21.8</td>
<td>91.3 to 125.7</td>
</tr>
</tbody>
</table>

*Diff:* Observed difference between means as % of reference mean

*Stat:* P value statistic

*n.s.d.:* no significant difference

*90% Sym CI:* 90% confidence interval based on 2 one-sided t-tests (α=0.05) expressed as % of reference mean + 100%

*90% Shortest CI:* 90% confidence interval based on 2 one-sided t-tests (α=0.05) expressed as % of reference mean + 100%

### Study Conclusions

The results demonstrated that Nolvadex 20 mg and the applicant’s tamoxifen formulation are bio-equivalent for tamoxifen. Bio-equivalence for the metabolite N-desmethyltamoxifen is also suggested by the results of this study.

### IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for applications of this type.

### IV.4 Clinical efficacy

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

### IV.5 Clinical safety

No clinical safety data is required for this application.

### IV.6 Discussion on the clinical aspects

The data presented demonstrates the bio-equivalence of the proposed product to the reference Nolvadex 20 mg Tablets. With reference to the CPMP Note for Guidance on the Investigation of Bio-availability and Bioequivalence (CPMP/EWP/QWP/1401/98), the bioequivalence study seems well designed, conducted, analysed, and reported.

The grant of a Marketing Authorisation is recommended.

### V User consultation

The SmPC, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. 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 the package leaflet contains.
VI OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Tamoxifen 20 mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

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

CLINICAL
The efficacy of tamoxifen is well established.

The SmPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, no significant non-clinical or clinical concerns were identified, and benefit has been shown to be associated with tamoxifen. The benefit risk is therefore considered to be positive.
Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels
The Summaries of Product Characteristics and Patient Information Leaflets (PIL) are consistent with the details registered for the cross-reference products.

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

The current approved labelling mock-up is presented below:
Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>06/07/2018</td>
<td>Type IB</td>
<td>To update SmPC sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.7, 4.8 and 5.1 and patient information leaflet (PIL) sections 2, 3 and 4 in line with Quality Review of Documents (QRD) template and the reference product; Nolvadex D Tablets (PL 17901/0033-4; AstraZeneca, UK), date of revision 05 April 2018.</td>
<td>Approved</td>
</tr>
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</table>
ANNEX 1

Our Reference: PL 20395/0010 - 50
Product: Tamoxifen 20 mg Tablets
Marketing Authorisation Holder: Relonchem Limited
Active Ingredient(s): Tamoxifen citrate
Submission Type: Variation
Submission Category: Type IB

Supporting evidence
To update SmPC sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.7, 4.8 and 5.1 and PIL sections 2, 3 and 4 in line with QRD template and the reference product; Nolvadex D Tablets (PL 17901/0033-4; AstraZeneca, UK), date of revision 05 April 2018.

Evaluation
The amended section of the SmPC and PIL are satisfactory.

Conclusion
The proposed changes are acceptable. The updated SmPC and PIL have been submitted and are acceptable.

In accordance with Directive 2010/84/EU, the current granted UK SmPC and PIL are available on the MHRA website.

Decision
Grant

Date: 24 September 2018