Public Assessment Report

Decentralised Procedure

Lecaent 25 mg Capsules, Hard
Lecaent 50 mg Capsules, Hard
Lecaent 75 mg Capsules, Hard
Lecaent 100 mg Capsules, Hard
Lecaent 150 mg Capsules, Hard
Lecaent 200 mg Capsules, Hard
Lecaent 225 mg Capsules, Hard
Lecaent 300 mg Capsules, Hard

(pregabalin)

Procedure No: UK/H/5800/001-008/DC

UK Licence No: PL 24668/0265-272

Caduceus Pharma Limited
LAY SUMMARY

Lecaent 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg Capsules, Hard
(pregabalin, hard capsule, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg)

This is a summary of the Public Assessment Report (PAR) for Lecaent 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg Capsules, Hard (PL 24668/0265-0272; UK/H/5800/001-008/DC).

It explains how Lecaent 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg Capsules, Hard 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 Lecaent 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg Capsules, Hard.

These products will collectively be referred to as Lecaent throughout the remainder of this public assessment report (PAR).

For practical information about using Lecaent, patients should read the package leaflet or contact their doctor or pharmacist.

What is Lecaent and what is it used for?
Lecaent is a ‘generic medicine’. This means that Lecaent is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Lyrica 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules (Pfizer Limited, UK).

Lecaent is used to treat epilepsy and Generalised Anxiety Disorder (GAD) in adults:

Epilepsy
Lecaent is used to treat a certain form of epilepsy (partial seizures with or without secondary generalisation in adults). The patient’s doctor will prescribe Lecaent to help treat the patient’s epilepsy when the patient’s current treatment is not controlling their condition. The patient should always take Lecaent in addition to the patient’s current treatment. Lecaent is not intended to be used alone, but should always be used in combination with other anti-epileptic treatment.

Generalised Anxiety Disorder
Lecaent is used to treat Generalised Anxiety Disorder (GAD). The symptoms of GAD are prolonged excessive anxiety and worry that are difficult to control. GAD can also cause restlessness or feeling keyed up or on edge, being easily fatigued (tired), having difficulty concentrating or mind going blank, feeling irritable, having muscle tension or sleep disturbance. This is different to the stresses and strains of everyday life.

How does Lecaent work?
Lecaent contains the active ingredient pregabalin, which belongs to a group of medicines called antiepileptics. The way in which pregabalin works is not fully understood, it is thought to work by binding to calcium channels found on nerve cells in the brain and spinal cord. This reduces the release of various neurotransmitters from these nerve cells.

Neurotransmitters are natural body chemicals that are stored in nerve cells. They are involved in transmitting messages between the nerve cells.

How is Lecaent used?
The pharmaceutical form of Lecaent is a capsule (hard) and the route of administration is by mouth (oral).
The patient must always take Lecaent exactly as their doctor has told them to. The patient must check with their doctor or pharmacist if they are not sure.

Lecaent is for oral use only.

The patient must take the number of capsules as instructed by the patient’s doctor. The dose, which has been adjusted for the patient and the patient’s condition, will generally be between 150 mg and 600 mg each day.

The patient’s doctor will tell the patient to take Lecaent either twice or three times a day.

For twice a day:
- The patient should take Lecaent once in the morning and once in the evening, at about the same time each day.

For three times a day:
- The patient should take Lecaent once in the morning, once in the afternoon and once in the evening, at about the same time each day.

If the patient has the impression that the effect of Lecaent is too strong or too weak, the patient should talk to their doctor or pharmacist.

The patient should swallow the capsule whole with water. The patient should continue taking Lecaent until the patient’s doctor tells the patient to stop.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

**What benefits of Lecaent have been shown in studies?**
Because Lecaent is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Lyrica 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules (Pfizer Limited, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Lecaent tablets?**
Because Lecaent is a generic medicine and is bioequivalent to the reference medicine Lyrica 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules (Pfizer Limited, UK), its benefits and possible side effects are taken as being the same as the reference medicine. For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Lecaent, see section 4 of the package leaflet available on the MHRA website.

**Why was Lecaent approved?**
It was concluded that, in accordance with EU requirements, Lecaent has been shown to have comparable quality and to be bioequivalent to Lyrica 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules (Pfizer Limited, UK). Therefore, the MHRA decided that, as for Lyrica 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules (Pfizer Limited, UK); 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 Lecaent?
A risk management plan (RMP) has been developed to ensure that Lecaent is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Lecaent including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Lecaent
The marketing authorisations for Lecaent were granted in the UK on 16 February 2015.

The full PAR for Lecaent follows this summary.

For more information about use of Lecaent, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in April 2015.
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<td>Overall conclusion, benefit/risk assessment</td>
<td>16</td>
</tr>
<tr>
<td>and recommendation</td>
<td></td>
</tr>
</tbody>
</table>
I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Caduceus Pharma Ltd Marketing Authorisations for the medicinal products Lecaent 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg Capsules, Hard (PL 24668/0265-0272; UK/H/5800/001-008/DC) on 16 February 2015. The products are prescription-only (POM) medicines indicated for:

**Epilepsy**
- Lecaent is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

**Generalised Anxiety Disorder**
- Lecaent is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

These applications were submitted using the Decentralised Procedure, with the UK as Reference Member State (RMS) and Iceland as Concerned Member State (CMS). The applicant subsequently withdrew the applications in Iceland during the procedure, leaving no CMS. The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products for these applications are Lyrica 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules which were first licenced to Pfizer Limited, UK (EU/1/04/279/001-005, EU/1/04/279/026 and EU/1/04/279/036) on 08 July 2004 via the Centralised Procedure.

The active substance, pregabalin, is a gamma-aminobutyric acid analogue ((S)-3-(aminomethyl)-5-methylhexanoic acid). The exact cellular mechanism of pregabalin action is not fully understood, but evidence from several studies suggests that it binds with high affinity to the α_2-δ subunits of the presynaptic neuron's voltage-gated calcium channels. Thus, the compound reduces depolarization-induced calcium influx at nerve terminals, and thereby reduces the release of several excitatory neurotransmitters, such as noradrenalin, glutamate, substance P and calcitonin gene-related peptide which have been involved in pain mechanisms.

Two bioequivalence studies were submitted to support these applications comparing the applicant’s test products Lecaent 50mg and 300 mg Capsules, Hard (Caduceus Pharma Limited) with the reference products Lyrica 50 mg and 300 mg hard capsules (Pfizer Limited, UK) under fasting conditions. The applicant has stated that the bioequivalence studies were conducted in compliance with Good Clinical Practice and Good Laboratory Practice.

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that these applications were based on a product being a generic medicinal product of an originator product that has been in clinical use 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.
II QUALITY ASPECTS

II.1 Introduction
Each capsule, hard contains 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg or 300 mg of the active ingredient pregabalin. Other ingredients consist of the pharmaceutical excipients mannitol, co-processed corn starch, (consisting of corn starch, pregelatinised corn starch), talc, gelatin, titanium dioxide (E171), and black printing ink (consisting of shellac, black iron oxide (E172) and potassium hydroxide). The 75 mg, 100 mg, 200 mg, 225 mg and 300 mg strength capsules, hard also contain red iron oxide (E172).

All strengths of the finished product are packed into aluminium/polyvinyl chloride (PVC) blister packs containing:
- The 25 mg strength is available in pack sizes of 56 and 84 capsules, hard
- The 50 mg, 100 mg and 200 mg strengths are available in pack size of 84 capsules, hard
- The 75, 150 mg, 225 mg and 300 mg mg strengths are available in a pack size of 56 capsules, hard

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2. Drug Substance
INN: Pregabalin.
Chemical names:

\[(S)-3-(Aminomethyl)-5-methylhexanoic acid\]
\[(S)-(+)\text{-}4\text{-}amino\text{-}3\text{-}(2\text{-}methylpropyl)\text{butanoic acid;}\]
\[(S)-(+)\text{-}3\text{-}isobutyl\text{-}\gamma\text{-}aminobutyric acid\]

Structural formula:

\[\text{HO} \quad \text{NH}_2 \quad \text{K} \]

Molecular formula: \(C_8H_{17}NO_2\).
Molecular mass: 159.23 g/mol
Appearance: A white or almost white crystalline powder.
Solubility: Sparingly soluble in water, slightly soluble in methanol and practically insoluble in acetone and isopropanol.

Pregabalin is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active 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.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.
An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Satisfactory certificates of analysis have been provided for all working standards. Batch analyses data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

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 development programme was to formulate safe, efficacious, capsules, hard containing 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg or 300 mg pregabalin per capsule, hard that are generics of the reference products Lyrica 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules (Pfizer Limited). A satisfactory account of the pharmaceutical development has been provided.

Comparative impurity and in-vitro dissolution profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of co-processed starch and black printing ink which are controlled to suitable in-house specifications. The applicant has also provided confirmation that red iron oxide (E172) present in the 75 mg, 100 mg, 200 mg, 225 mg and 300 mg strength capsules and black iron oxide (E172) [present in the black printing ink] comply with Directive 2008/128/EC (which lays down purity criteria concerning colours for use in foodstuffs). Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that they are manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of these products.

Manufacture of the product

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot-scale batch sizes and shown satisfactory results. The marketing authorisation holder (MAH) has committed to perform additional process validation studies on future commercial-scale batches.

Finished Product Specification

The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.
Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of the 25 mg, 50 mg, 75 mg and 300 mg strengths of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 18 months for the 25 mg and 50 mg strengths and 2 years for the 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg strengths with the storage conditions ‘Do not store above 30°C’.

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
There are no objections to the approval of these applications from a pharmaceutical viewpoint.
III  NON-CLINICAL ASPECTS

III.1  Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of pregabalin 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.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

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.

Impurities
Impurity limits in the drug substance specification were set in accordance with current ICH guidelines for impurities in new drug substances (ICHQ3A(R2)) and for residual solvents (ICHQ3C(R4)). With a maximum daily dose of 600 mg of pregabalin the qualification threshold is 0.15%. There are no issues from a toxicological perspective.

The residual solvents are controlled in line with ICH QC3(R5).

Based on the a maximum daily dose of 600 mg per day; the proposed limits are in compliance with the requirements of ICHQ3B(R2) - Impurities in New Drug Products.

III.5  Ecotoxicity/environmental risk assessment (ERA)
Since Lecaent is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6  Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV  CLINICAL ASPECTS

IV.1  Introduction
The clinical pharmacology of pregabalin is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamic or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of pregabalin.
Based on the data provided, Lecaent can be considered bioequivalent to Lyrica 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules (Pfizer Limited, UK).

IV.2 Pharmacokinetics

In support of these applications, the applicant submitted the following bioequivalence studies:

STUDY 1

An open label, randomised, two-period, two-treatment, two-sequence, single dose, crossover study to compare the pharmacokinetics of the applicant’s test product Lecaent 50mg Capsules, Hard (Caduceus Pharma Limited) versus the reference product, Lyrica 50 mg hard capsules (Pfizer Limited, UK), in healthy adult subjects under fasting conditions.

The subjects were administered a single dose (50 mg) of either the test or the reference product with 240 ml of water after an overnight fast. Water was not permitted 1 hour before dosing and until 1 hour post dosing. The subjects were served a meal at 4 hours post-dose.

Blood samples were collected for plasma levels before dosing and up to and including 48 hours after each administration. The washout period between the treatment phases was 8 days. The pharmacokinetic results are presented below:

Table: Summary of geometric means and 90% confidence intervals for test and reference product for pregabalin.

<table>
<thead>
<tr>
<th>treatment</th>
<th>(\text{AUC}_{0-t})</th>
<th>(\text{AUC}_{0-\infty})</th>
<th>(\text{C}_{\text{max}})</th>
<th>(\text{ratio} \ \text{AUC}<em>{0-t} / \ \text{AUC}</em>{0-\infty} \ (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>reference</td>
<td>11.357</td>
<td>11.732</td>
<td>1.847</td>
<td>96.798</td>
</tr>
<tr>
<td>SD</td>
<td>1.315</td>
<td>1.347</td>
<td>0.440</td>
<td>1.574</td>
</tr>
<tr>
<td>test</td>
<td>11.486</td>
<td>11.907</td>
<td>1.886</td>
<td>96.429</td>
</tr>
<tr>
<td>SD</td>
<td>1.397</td>
<td>1.396</td>
<td>0.410</td>
<td>2.113</td>
</tr>
</tbody>
</table>

**Table 3 Summary pharmacokinetics for pregabalin**

<table>
<thead>
<tr>
<th>parameter</th>
<th>(\text{ratio} \ \text{test/reference} \ (%))</th>
<th>lower bound</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{AUC}_{0-t})</td>
<td>101.02</td>
<td>98.40</td>
<td>103.71</td>
</tr>
<tr>
<td>(\text{C}_{\text{max}})</td>
<td>102.57</td>
<td>95.99</td>
<td>109.61</td>
</tr>
</tbody>
</table>

**Table 6 Estimates of test/reference \(\text{AUC}_{0-t}/\text{C}_{\text{max}}\) ratio with the 90% CI.**

AUC\(_{0-\infty}\) area under the plasma concentration-time curve from time zero to infinity
AUC\(_{0-t}\) area under the plasma concentration-time curve from zero to t hours
\(\text{C}_{\text{max}}\) maximum plasma concentration
\(\text{t}_{\text{max}}\) time until \(\text{C}_{\text{max}}\) is reached

STUDY 2

An open label, randomised, two-period, two-treatment, two-sequence, single dose, crossover study to compare the pharmacokinetics of the applicant’s test product Lecaent 300mg Capsules, Hard (Caduceus Pharma Limited) versus the reference product, Lyrica 300 mg hard capsules (Pfizer Limited, UK), in healthy adult subjects under fasting conditions.
The subjects were administered a single dose (300 mg) of either the test or the reference product with 240 ml of water after an overnight fast. Water was not permitted 1 hour before dosing and until 1 hour post dosing. The subjects were served a meal at 4 hours post-dose.

Blood samples were collected for plasma levels before dosing and up to and including 48 hours after each administration. The washout period between the treatment phases was 9 days. The pharmacokinetic results are presented below:

### Table: Summary of geometric means and 90% confidence intervals for test and reference product for pregabalin.

<table>
<thead>
<tr>
<th>treatment</th>
<th>( \text{AUC}_{0-t} )</th>
<th>( \text{AUC}_{0-\infty} )</th>
<th>( \text{C}_{\text{max}} )</th>
<th>( \text{ratio} \ \frac{\text{AUC}<em>{0-t}}{\text{AUC}</em>{0-\infty}} ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>reference</td>
<td>67.048</td>
<td>67.582</td>
<td>8.555</td>
<td>99.242</td>
</tr>
<tr>
<td>SD</td>
<td>10.735</td>
<td>10.992</td>
<td>1.684</td>
<td>0.403</td>
</tr>
<tr>
<td>test</td>
<td>66.702</td>
<td>67.227</td>
<td>8.556</td>
<td>99.250</td>
</tr>
<tr>
<td>SD</td>
<td>10.375</td>
<td>10.633</td>
<td>1.435</td>
<td>0.383</td>
</tr>
</tbody>
</table>

**Table 9 Summary pharmacokinetics for pregabalin**

<table>
<thead>
<tr>
<th>parameter</th>
<th>ratio test/reference ( % )</th>
<th>lower bound</th>
<th>upper bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{AUC}_{0-t} )</td>
<td>99.57</td>
<td>97.85</td>
<td>101.32</td>
</tr>
<tr>
<td>( \text{C}_{\text{max}} )</td>
<td>100.56</td>
<td>95.51</td>
<td>105.88</td>
</tr>
</tbody>
</table>

**Table 12 Estimates of test/reference \( \frac{\text{AUC}_{0-t}}{\text{C}_{\text{max}}} \) ratio with the 90% CI.**

AUC\( _{0-\infty} \) area under the plasma concentration-time curve from time zero to infinity

AUC\( _{0-t} \) area under the plasma concentration-time curve from zero to \( t \) hours

\( C_{\text{max}} \) maximum plasma concentration

\( t_{\text{max}} \) time until \( C_{\text{max}} \) is reached

**Conclusion**

The 90% confidence intervals of the test/reference ratio for AUC and \( C_{\text{max}} \) values for pregabalin for the 50 mg and 300 mg strengths lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s 50 mg and 300 mg test products are bioequivalent to the reference products Lyrica 50 mg and 300 mg hard capsules (Pfizer Limited, UK).

Although the 50 mg and 300 mg pregabalin capsule formulations are not dose-proportional, the 25 mg and 50 mg capsule strengths are dose-proportional; likewise the 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg strength capsules are also dose-proportional. Hence, the results and conclusions with the 50 mg capsule strength can be extrapolated to the 25 mg dosage form and the results and conclusions of the 300 mg capsule strength can be extrapolated to the 75 mg, 100 mg, 150 mg, 200 mg and 225 mg capsule strengths.

In summary, as the 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence studies with the 50 mg and 300 mg can be extrapolated to the 25 mg, 75 mg, 100 mg, 150 mg, 200 mg and 225 mg capsule strengths.

**IV.3 Pharmacodynamics**

No new pharmacodynamic data were submitted and none were required for an application of this type.
IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety
No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Lecaent.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Oedema and Oedema–related events</td>
<td></td>
</tr>
<tr>
<td>Dizziness, Somnolence, Loss of Consciousness, Syncope, and Potential for Accidental injury</td>
<td></td>
</tr>
<tr>
<td>Discontinuation Events</td>
<td></td>
</tr>
<tr>
<td>Drug interactions (lorazepam, ethanol, and CNS depressants)</td>
<td></td>
</tr>
<tr>
<td>Euphoria</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity and Allergic Reactions</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
</tr>
<tr>
<td>Vision-related events</td>
<td></td>
</tr>
<tr>
<td>Abuse, Misuse, and Drug Dependence</td>
<td></td>
</tr>
</tbody>
</table>

| Important potential risks                                                                 |                                                                             |
| Suicidality                                                                               |                                                                             |
| Haemangiosarcoma                                                                          |                                                                             |
| Off-label use in paediatric patients                                                       |                                                                             |

| Missing information                                                                       | Pregnancy and lactation                                                     |
Summary table of risk minimisation measures:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Summary of Routine Risk Minimisation Activities</th>
<th>Summary of Additional Risk Minimisation Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain</td>
<td>Routine risk minimisation measures are considered sufficient as information is included in section 4.8 of the SmPC</td>
<td>N/A</td>
</tr>
<tr>
<td>Peripheral Oedema and Oedema-related events</td>
<td>Routine risk minimisation measures are considered sufficient as information is included in section 4.8 of the SmPC</td>
<td>N/A</td>
</tr>
<tr>
<td>Dizziness, Somnolence, Loss of Consciousness, Syncope, and Potential for Accidental Injury</td>
<td>Routine risk minimisation measures are considered sufficient as information is included in sections 4.4, 4.7 and 4.8 of the SmPC</td>
<td>N/A</td>
</tr>
<tr>
<td>Discontinuation Events</td>
<td>Routine risk minimisation measures are considered sufficient as information is included in sections 4.4 and 4.8 of the SmPC</td>
<td>N/A</td>
</tr>
<tr>
<td>Drug interactions (lorazepam, ethanol, and CNS depressants)</td>
<td>Routine risk minimisation measures are considered sufficient as information is included in section 4.5 of the SmPC</td>
<td>N/A</td>
</tr>
<tr>
<td>Euphoria</td>
<td>Routine risk minimisation measures are considered sufficient as information is included in section 4.8 of the SmPC</td>
<td>N/A</td>
</tr>
<tr>
<td>Hypersensitivity and Allergic Reactions</td>
<td>Routine risk minimisation measures are considered sufficient as information is included in sections 4.3, 4.4 and 4.8 of the SmPC</td>
<td>N/A</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Routine risk minimisation measures are considered sufficient as information is included in sections 4.4 and 4.8 of the SmPC</td>
<td>N/A</td>
</tr>
<tr>
<td>Vision-related events</td>
<td>Routine risk minimisation measures are considered sufficient as information is included in sections 4.4 and 4.8 of the SmPC</td>
<td>N/A</td>
</tr>
<tr>
<td>Abuse, Misuse, and Drug Dependence</td>
<td>Routine risk minimisation measures are considered sufficient as information is included in sections 4.4 and 4.8 of the SmPC</td>
<td>N/A</td>
</tr>
</tbody>
</table>
In line with the reference product the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

**IV.7 Discussion on the clinical aspects**

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

Bioequivalence has been demonstrated between the applicant’s product Lecaent 50 mg and 300 mg capsules, Hard (Caduceus Pharma Limited) and the reference products, Lyrica 50 mg, and 300 mg hard capsules (Pfizer Limited, UK) respectively under fasting conditions.

As the 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the
bioequivalence studies with the 50 mg and 300 mg can be extrapolated to the 25 mg, 75 mg, 100 mg, 150 mg, 200 mg and 225 mg capsule strengths.

The grant of marketing authorisations is recommended for these applications.

V User consultation
The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the package leaflet was English.

The results show that the package 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.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with pregabalin is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

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.

The approved labelling for Lecaent is presented below:
PAR Lecaent 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg Capsules, Hard

UK/H/5800/001-008/DC