Public Assessment Report

Decentralised Procedure

Pregabalin Colonis 20 mg/ml Oral Solution

(pregabalin)

Procedure No: UK/H/6596/001/DC

UK Licence Number: PL 41344/0042

Colonis Pharma Ltd
LAY SUMMARY

Pregabalin Colonis 20 mg/ml Oral Solution

This is a summary of the Public Assessment Report (PAR) for Pregabalin Colonis 20 mg/ml Oral Solution (PL 41344/0042; UK/H/6596/001/DC). It explains how Pregabalin Colonis 20 mg/ml Oral Solution 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 Pregabalin Colonis 20 mg/ml Oral Solution.

The product will be referred to as ‘Pregabalin Oral Solution’ throughout the remainder of this lay summary.

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

What is Pregabalin Oral Solution and what is it used for?
Pregabalin Oral Solution is a ‘generic medicine’. This means that Pregabalin Oral Solution is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Lyrica 20 mg/ml Oral Solution (Pfizer Limited).

Pregabalin Oral Solution belongs to a group of medicines used to treat epilepsy and Generalised Anxiety Disorder (GAD) in adults.

Pregabalin Oral Solution is used in adults as described below:

Epilepsy
Pregabalin Oral Solution is used to treat a certain form of epilepsy (partial seizures with or without secondary generalisation- epileptic fits starting on one specific part of the brain) in adults. The patient’s doctor will prescribe Pregabalin Oral Solution to help treat epilepsy when the patient’s current treatment is not controlling their condition. Pregabalin Oral Solution should be taken in addition to a patient’s current treatment. Pregabalin Oral Solution is not intended to be used alone, but should always be used in combination with other anti-epileptic treatment.

Generalised Anxiety Disorder
Pregabalin Oral Solution 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 Pregabalin Oral Solution work?
Pregabalin Oral Solution contains the active substance pregabalin. Pregabalin belongs to a group of medicines called ‘antiepileptics’. It works by slowing down impulses in the brain that cause seizures. Pregabalin also affects chemicals in the brain that send pain signals across the nervous system.

How is Pregabalin Oral Solution used?
The pharmaceutical form of this medicine is an oral solution and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.
The patient’s doctor will determine what dose is appropriate for them.

**Epilepsy or Generalised Anxiety Disorder:**
- The solution should be taken as instructed the doctor.
- The dose will be adjusted for the patient and their condition and will generally be between 150 mg (7.5 ml) and 600 mg (30 ml) each day.
- The doctor will tell their patient to take Pregabalin Oral Solution either twice or three times a day. For twice a day Pregabalin Oral Solution should be taken once in the morning and once in the evening, at about the same time each day. For three times a day it should be taken 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 Pregabalin Oral Solution is too strong or too weak, they should talk to their doctor or pharmacist.

Elderly patients (over 65 years of age), should take Pregabalin Oral Solution normally except if they have kidneys problems. The doctor may prescribe a different dosing schedule and/or dose if the patient has problems with their kidneys.

This medicine should continue to be taken until the doctor tells the patient to stop.

Section 3 of the package leaflet provides detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Pregabalin Oral Solution is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

**What are the possible side effects of Pregabalin Oral Solution?**
Because Pregabalin Oral Solution is a generic medicine and is comparable to the reference medicine Lyrica 20 mg/ml Oral Solution (Pfizer Limited), the benefits and possible side effects are taken as being the same as for the reference medicine.

For the full list of restrictions, see the package leaflet.

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

**Why was Pregabalin Oral Solution approved?**
In accordance with EU requirements it was concluded that, Pregabalin Oral Solution has comparable quality and it is considered to be bioequivalent to Lyrica 20 mg/ml Oral Solution (Pfizer Limited); similarly to Lyrica 20 mg/ml Oral Solution (Pfizer Limited) its benefits are greater than the risks and it is, therefore, recommended that Pregabalin Oral Solution can be approved for use.
What measures are being taken to ensure the safe and effective use of Pregabalin Oral Solution?
A risk management plan (RMP) has been developed to ensure that Pregabalin Oral Solution is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Pregabalin Oral Solution 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 and reviewed continuously.

Other information about Pregabalin Oral Solution
Italy, and the UK agreed to grant a Marketing Authorisation on 12 March 2018. Following a subsequent national phase, a Marketing authorisation was granted in the UK on 9 April 2018.

The full PAR for Pregabalin Oral Solution follows this summary.

For more information about treatment with Pregabalin Oral Solution, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in June 2018.
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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) granted Colonis Pharma Limited, a marketing authorisation for the medicinal product Pregabalin Colonis Oral Solution (PL 41344/0042; UK/H/6596/001/DC). This product is a prescription-only medicine (POM).

Pregabalin Oral Solution is indicated for:

**Epilepsy**
Pregabalin Colonis Oral Solution is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

**Generalised Anxiety Disorder**
Pregabalin Colonis Oral Solution is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Italy as a Concerned Member State (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Lyrica 20 mg/ml Oral Solution (EU/1/04/279/044) which was granted to Pfizer Limited on 06 July 2004 via the centralised procedure.

Pregabalin belongs to the pharmacotherapeutic group antiepileptics/other antiepileptics. The active substance is pregabalin - a gamma-aminobutyric acid analogue ((S)-3-(aminomethyl)-5-methylhexanoic acid), which binds to an auxiliary subunit (α2-δ protein) of voltage-gated calcium channels in the central nervous system. The α2δ subunits enhance the trafficking of α1-subunits and decrease their turnover at the plasma membrane. Pregabalin attenuates calcium influx currents leading to decreased release of excitatory neurotransmitters such as glutamate, norepinephrine and substance P content from nerve terminals. Pregabalin has a higher intrinsic activity at the α2δ subunit of voltage-gated calcium channels compared to gabapentin, corresponding to a higher potency in rodent antiepileptic activity. This is thought to explain its superiority in human seizure control (including patients uncontrolled by gabapentin).

No new non-clinical studies were submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new clinical data have been submitted and none are required for an application of this type. A bioequivalence study was not necessary to support this application as both test and reference product are oral solutions at the time of administration.

The RMS 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, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considered that the application could be approved at the end of procedure on 12 March 2018. After a subsequent national phase, a licence was granted in the UK on 9 April 2018.
II QUALITY ASPECTS

II.1 Introduction
Each ml of solution contains 20 mg of pregabalin. The excipients present are methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), sodium dihydrogen phosphate dihydrate, disodium phosphate, anhydrous (E339), sucralose (E955), strawberry flavour sodium hydroxide (for pH adjustment), and purified water.

The finished product is packed in a white HDPE bottle containing 250 ml of oral solution in a cardboard carton. The carton contains one HDPE bottle or two HDPE bottles of 250 ml nominal capacity with HDPE - lined tamper evident and child-resistant screw caps. The carton also contains a 5 ml, CE marked oral syringe with intermediate graduations of 0.25 ml and one or two press-in bottle adaptors (PIBA).

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

II.2 Drug Substance
INN: Pregabalin
Chemical name: (3S)-3-(Aminomethyl)-5-methylhexanoic acid
Structure:

![Structure of Pregabalin]

Molecular formula: C₈H₁₇CO₂
Molecular weight: 159.23 g/mol
Appearance: White to off-white crystalline powder.
Solubility: Sparingly soluble in water, very slightly soluble in methanol, practically insoluble in heptane.

Pregabalin is the subject of an active substance master file (ASMF).

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.

Batch analyses data are provided that comply with the proposed specification.
Satisfactory Certificates of Analysis have been provided for all working standards used.

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 develop a safe, efficacious, oral solution containing 20 mg pregabalin per ml of oral solution that is comparable in performance to the reference product Lyrica 20 mg/ml Oral Solution (Pfizer Limited). The development of the product has been described, the choice of excipients is justified, and their functions explained.

All excipients used apart from the strawberry flavouring, comply with their respective European Pharmacopeia monographs. The strawberry flavouring adheres to its in house specifications.

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

None of the excipients used in this product contain material of animal or human origin.

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

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the product, together with an appropriate account of the manufacturing process. Process validation data on commercial scale batches have been provided. The results are satisfactory.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data complying with the release specification have been provided. 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 finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 36 months for the unopened bottle and an in-use shelf-life of 3 months with the storage condition ‘Do not store above 25°C’.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application 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.

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

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction
The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of pregabalin are well known. A comprehensive review of the published literature has been provided by the applicant. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
In accordance with the guidance on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) “A waiver of the need to provide equivalence data may be acceptable in the case of solutions, e.g. eye drops, nasal sprays or cutaneous solutions, if the test product is of the same type of solution (aqueous or oily), and contains the same concentration of the same active substance as the medicinal product currently approved”, therefore no bioequivalence study was submitted, and this is acceptable for this aqueous solution of equal strength (20 mg/ml), containing the same active substance (Lyrica 20 mg/ml Oral Solution) as the reference product. Therefore, the criteria for biowaiver are fulfilled. No biostudy is required to compare the bioequivalence of the two products.

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 are required.

IV.6  Risk Management Plan (RMP) and Pharmacovigilance System
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended.

A summary of safety concerns as approved in the RMP are listed below:

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<th>Important potential risks</th>
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<td>Weight gain</td>
<td>Cancer of the blood vessels</td>
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<td>Swelling (oedema) of the body, including in the extremities</td>
<td>Thoughts of self-harming or suicide</td>
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<td>Dizziness, sleepiness, loss of consciousness, fainting, and potential for accidental injury</td>
<td>Off label use in children</td>
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<td>Events after pregabalin discontinuation</td>
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<td>Interactions with other medicines</td>
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<td></td>
<td>Euphoria</td>
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<td>Hypersensitivity reactions, including allergic reactions</td>
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<td>Congestive heart failure</td>
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<td>Vision-related events</td>
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<td>Abuse, misuse and drug dependence</td>
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IV.7  Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application from a clinical viewpoint.

V  User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Pregabalin Focus 20 mg/ml oral solution. The PIL has been harmonised with the PIL for the reference product Lyrica 20 mg/ml Oral Solution (EU/1/04/279/044; Pfizer Limited). The bridging report submitted by the applicant is acceptable.

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 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 MAH has submitted the following approved labelling for this medicine which is presented below:
PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL ON GLASS BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Pregabalin Colonis 20mg/ml Oral Solution

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml of oral solution contains 20 mg pregabalin.

3. LIST OF EXCIPIENTS

The product also contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216). See the leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution

2 x 250 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:
9. **SPECIAL STORAGE CONDITIONS**

This medicinal product does not require any special storage conditions.

After first opening do not store above 25° C and use within 3 months.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Colonis Pharma Ltd  
Quantum House,  
Hobson Industrial Estate,  
County Durham, Burnopfield  
NE16 6EA, United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 41344/0042

13. **BATCH NUMBER**

Lot:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Under medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**
1. **NAME OF THE MEDICINAL PRODUCT**

   Pregabalin Colonis 20mg/ml Oral Solution

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

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16. **INFORMATION IN BRAILLE**
PARTICULARS TO APPEAR ON THE OUTER PACKAGING BOX

1. NAME OF THE MEDICINAL PRODUCT

Pregabalin Colonis 20mg/ml Oral Solution

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml of oral solution contains 20 mg pregabalin.

3. LIST OF EXCIPIENTS

The product also contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216). See the leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution

2 x 250 ml
This pack contains 2 adaptors and 1 administration oral syringe.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

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After first opening do not store above 25°C and use within 3 months.
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16. **INFORMATION IN BRAILLE**

Pregabalin Colonis 20mg/ml Oral Solution

17. **UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included

18. **UNIQUE IDENTIFIER – HUMAN READABLE DATA**

PC: <to be completed nationally>

SN: <to be completed nationally>

NN: <to be completed nationally>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING BOX

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1 x 250 ml
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NN: <to be completed nationally>
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)

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