Public Assessment Report

Decentralised Procedure

METHYLPREDNISOLONE 500 MG POWDER AND SOLVENT FOR SOLUTION FOR INJECTION/INFUSION

METHYLPREDNISOLONE 1000 MG POWDER AND SOLVENT FOR SOLUTION FOR INJECTION/INFUSION

(Methylprednisolone sodium succinate)

Procedure No: UK/H/4085/001-2/DC

UK Licence No: PL 18157/0227-8

BEACON PHARMACEUTICALS LTD
LAY SUMMARY

Methylprednisolone 500 mg powder and solvent for solution for injection/infusion

Methylprednisolone 1000 mg powder and solvent for solution for injection/infusion

(Methylprednisolone sodium succinate, powder and solvent for solution for injection/infusion, 500 mg or 1000 mg of methylprednisolone per vial)

This is a summary of the Public Assessment Report (PAR) for Methylprednisolone 500 mg powder and solvent for solution for injection/infusion and Methylprednisolone 1000 mg powder and solvent for solution for injection/infusion. It explains how Methylprednisolone 500 mg and 1000 mg powder and solvent for solution for injection/infusion 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 Methylprednisolone 500 mg and 1000 mg powder and solvent for solution for injection/infusion.

The products will be collectively referred to as Methylprednisolone throughout the remainder of this lay summary.

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

What is Methylprednisolone and what is it used for?
Methylprednisolone is a ‘generic medicine’. This means that Methylprednisolone is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Solu-Medrone 500 mg powder for injection (Pharmacia Limited, UK).

Methylprednisolone belongs to a group of medicines called corticosteroids (steroids). Corticosteroids are produced naturally in the body and are important for many body functions.

Boosting a patient’s body with extra corticosteroid such as Methylprednisolone can help following surgery (e.g. organ transplants), flare-ups of the symptoms of multiple sclerosis or other stressful conditions. These include inflammatory or allergic conditions affecting the:
- brain caused by a tumour or meningitis
- bowel and gut e.g. ‘Crohn’s disease’ and ‘ulcerative colitis’
- lungs caused by asthma, severe allergy or hypersensitivity, tuberculosis or breathing in (aspirating) vomit or stomach contents
- skin, e.g. Stevens-Johnson Syndrome.

Methylprednisolone may be prescribed to treat conditions other than those listed above. The patient should ask their doctor if they are unsure why they have been given this medicine.

How does Methylprednisolone work?
The active ingredient, methylprednisolone, is similar to natural hormones called corticosteroids (steroids) produced by the adrenal glands. They work by damping down inflammation and excessive activity of the immune system.
How is Methylprednisolone used?
The pharmaceutical form of this medicine is a powder and solvent for solution for injection/infusion and the route of administration is either into a vein (intravenous) or into a muscle (intramuscular).

The patient’s doctor will decide on the site of injection, how many injections they will receive depending on the condition being treated and its severity. The patient’s doctor will inject the lowest dose for the shortest possible time to get effective relief of their symptoms.

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

Do not drink grapefruit juice while being treated with Methylprednisolone.

Steroid Cards
The patient should remember to always carry a Steroid Treatment Card. Make sure the patient’s doctor or pharmacist has filled out the details of their medicine, including the dose and how long they will require steroid treatment.

The patient should show their steroid card to anyone who gives them treatment (such as a doctor, nurse or dentist) while they are taking this medicine, and for 3 months after their last injection.

If the patient is admitted to hospital for any reason, they must always tell their doctor or nurse that they are taking Methylprednisolone. The patient can also wear a medic-alert bracelet or pendant to let medical staff know that they are taking a steroid if they have an accident or become unconscious.

This medicine can only be obtained with a prescription.

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

What benefits of Methylprednisolone have been shown in studies?
No additional studies were needed as Methylprednisolone is a generic medicine that is given intravenously or intramuscularly and contains the same active substance as the reference medicine, Solu-Medrone 500 mg powder for injection (Pharmacia Limited, UK).

What are the possible side effects of Methylprednisolone?
Because Methylprednisolone is a generic medicine, 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 Methylprednisolone, see section 4 of the package leaflet available on the MHRA website.

Why was Methylprednisolone approved?
It was concluded that, in accordance with EU requirements, Methylprednisolone has been shown to have comparable quality and to be comparable to Solu-Medrone 500 mg powder for
injection (Pharmacia Limited, UK). Therefore, the MHRA decided that, as for Solu-Medrone 500 mg powder for injection (Pharmacia Limited, UK), the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Methylprednisole?
Safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Methylprednisole 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 Methylprednisole
Ireland and the UK agreed to grant Marketing Authorisations for Methylprednisole on 06 April 2011. Marketing Authorisations were granted in the UK on 07 June 2011.

The full PAR for Methylprednisole follows this summary.

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

This summary was last updated in May 2016.
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I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Methylprednisolone 500 mg and 1000 mg powder and solvent for solution for injection/infusion (PL 18157/0227-8; UK/H/4085/001-2/DC) could be approved. These applications were submitted by the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Ireland as Concerned Member State (CMS). These products are prescription-only medicines (POM).

Methylprednisolone 500 mg and 1000 mg powder and solvent for solution for injection/infusion is indicated to treat any condition in which rapid and intense corticosteroid effect is required such as:

- **Dermatological disease;**
  - Severe erythema multiforme (Stevens Johnson syndrome)

- **Allergic states;**
  - Bronchial asthma
  - Severe seasonal and perennial allergic rhinitis
  - Angioneurotic oedema
  - Anaphylaxis

- **Gastro intestinal diseases;**
  - Ulcerative colitis
  - Crohn's disease

- **Respiratory diseases;**
  - Aspiration of gastric contents
  - Fulminating or disseminated tuberculosis (with appropriate antituberculous chemotherapy)

- **Neurological disorders**
  - Cerebral oedema secondary to cerebral tumour
  - Acute exacerbations of multiple sclerosis superimposed on a relapsing/remitting background.

- **Miscellaneous;**
  - T.B. meningitis (with appropriate antituberculous chemotherapy)
  - Transplantation

These are applications made according to Article 10.1 of 2001/83/EC, as amended claiming to be generic medicinal products of Solu-Medrone 500 mg powder for injection, which was originally licensed to Pharmacia Limited, UK on 31 January 1972.

Methylprednisolone sodium succinate is a synthetic corticosteroid with mainly glucocorticoid activity which is used mostly short term in serious conditions to reduce inflammatory activity. Methylprednisolone comes in various forms such as the base, acetate salt and the sodium succinate ester (the subject of these applications). The latter form has the advantage of high water solubility which makes it particularly suitable for parenteral administration when a rapid and intense therapeutic effect is needed.

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

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 this product.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 06 April 2011. After a subsequent national phase, the licences were granted in the UK on 07 June 2011.
II QUALITY ASPECTS

II.1 Introduction

Each vial of powder contains 663.0 mg or 1326.0 mg methylprednisolone sodium succinate equivalent to 500 mg or 1000 mg of methylprednisolone. After reconstitution in water for injections, each ml of solution contains the equivalent of 59.6 mg of methylprednisolone. Each ampoule of solvent contains 7.8 ml (500 mg strength) or 15.6 ml (1000 mg strength) of water for injection. There are no pharmaceutical excipients in these products.

Each 500 mg strength cardboard carton contains:
Powder;
A Type I clear glass vial with butyl rubber plug and flip top seal. Each vial contains the equivalent of 500 mg of methylprednisolone as the sodium succinate for reconstitution with 7.8 ml of Water for Injections

Solvent;
A Type I clear glass ampoule containing 7.8 ml of Water for Injections.

Each 1000 mg strength cardboard carton contains:
Powder;
A Type I clear glass vial with butyl rubber plug and flip top seal. Each vial contains the equivalent of 1000 mg of methylprednisolone as the sodium succinate for reconstitution with 15.6 ml of Water for Injections.

Solvent;
A Type I clear glass vial with butyl rubber plug and flip top seal containing 15.6 ml of Water for Injections.

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: Methylprednisolone sodium succinate
Chemical name: Pregna-3,20-dione,21-(3-carboxy-1-oxopropoxy)-11,17-dihydroxy-6-methyl,monosodium salt
11,17,21-Trihydroxy-6-methylpregna-1,4-diene-3,20-dione 21-(sodium succinate)

Structure:

Molecular formula: C_{26}H_{33}NaO_{8}
Molecular mass: 496.53
Appearance:  Methylprednisolone sodium succinate is a white or almost white amorphous powder which is soluble in water.

Methylprednisolone sodium succinate is not the subject of a European Pharmacopoeia monograph.

Synthesis of the drug 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.

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.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and 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, stable products that could be considered generic medicinal products of the reference product Solu-Medrone 500 mg powder for injection (Pharmacia Limited, UK).

Details of the pharmaceutical development of the product have been supplied and are satisfactory.

Comparative impurity profiles have been provided for the proposed and originator products.

There are no pharmaceutical excipients in these products.

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 product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.
**Finished Product Specification**
The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 18 months for the unopened vial, with the storage instructions “Keep the vials in the outer carton in order to protect from light”

After reconstitution with sterile Water for Injections, the product must be used immediately with any remainder discarded.

**Bioequivalence/bioavailability**
No bioequivalence studies have been submitted and none are required to support applications of this type.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPCs, PIL and labels are acceptable.

**MAA forms**
The MAA forms are satisfactory.

**Expert report**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**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 methylprednisolone are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology 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)
A suitable justification has been provided for non-submission of an environmental risk assessment. As these products are intended for generic substitution with a currently marketed brand leader, i.e. no increase in environmental burden is anticipated, the justification is accepted.

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

III.3 CLINICAL ASPECTS
Introduction
In accordance with Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) a bioequivalence study is not requested if the product is an aqueous intravenous solution containing the same active substance in the same concentration as the currently licensed product.

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 methylprednisolone.

IV.2 Pharmacokinetics
In accordance with Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) a bioequivalence study is not requested if the product is an aqueous intravenous solution containing the same active substance in the same concentration as the currently licensed product.

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 these applications.

IV.5 Clinical safety
No new safety data were submitted and none were required for these applications.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPCs, PIL and labels are acceptable. The SmPC is consistent with that for the originator product. The PIL is consistent with the SmPC and in-line with current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

IV.6 Pharmacovigilance System and Risk Management Plan
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person 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.
A suitable justification has been provided for not submitting a risk management plan for this application.

IV.7 Discussion on the clinical aspects
There are no objections to the approval of these applications from a clinical viewpoint.

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 PIL 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 important quality characteristics of Methylprednisolone 500 mg and 1000 mg powder and solvent for solution for injection/infusion 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.

EFFICACY
No new efficacy data were submitted and none were required for these applications.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with methylprednisolone 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 this medicine is presented below:
Methylprednisolone 500mg powder for solution for injection/infusion
Methylprednisolone (as sodium succinate)
For intramuscular or intravenous use. Read the package leaflet before use. Use the reconstituted solution immediately and discard any remainder.
Beacon Pharmaceuticals Ltd. PL 18157/0227 PA 1312/10/1

Water for Injections labelling:

To be used for reconstitution.
Discard any remaining unused solution.
Beacon Pharmaceuticals Ltd
PL 18157/0227 PA 1312/10/1
PAR Methylprednisolone 500 mg and 1000 mg powder and solvent for solution for injection/infusion
Methylprednisolone (as sodium succinate)

Beacon

Methylprednisolone 1000mg powder and solvent for solution for injection/infusion
Methylprednisolone (as sodium succinate)

1000mg
One vial of powder and one vial of solvent

POM

Methylprednisolone 1000mg powder and solvent for solution for injection/infusion
Methylprednisolone (as sodium succinate)

Methylprednisolone sodium succinate equivalent to 1000mg methylprednisolone.
Exipients: sodium phosphate dibasic. Each vial of powder contains methylprednisolone sodium succinate equivalent to 1000mg methylprednisolone. Each vial of solvent contains 15.6ml of water for injections. For intramuscular injection, intravenous injection or intravenous infusion.
Read the package leaflet before use. Dilute only with the diluents listed in the package leaflet.
Keep out of the reach and sight of children.
Keep the vial in the outer carton to protect from light. Use the reconstituted solution immediately and discard any remainder.
Beacon Pharmaceuticals Ltd.,
85 High St., Tunbridge Wells, TN1 1YG, UK.
PL 18157/0228 PA 1312/10/2
Vial label:

**Methylprednisolone 1000mg powder for solution for injection/infusion**

**Methylprednisolone (as sodium succinate)**

For intramuscular or intravenous use. Read the package leaflet before use. Use the reconstituted solution immediately and discard any remainder.

Beacon Pharmaceuticals Ltd. PL 18157/0228 PA 1312/10/2

Water for Injections labelling:

**Water for injections.**

15.6ml

To be used for reconstitution. Discard any remaining unused solution.

Beacon Pharmaceuticals Ltd
PL 18157/0228 PA 1312/10/2
**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

The following table lists non-safety variations of clinical significance to the Marketing Authorisations for these products that have been approved by the MHRA since the products were first licensed. The table includes updates that have been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

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<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
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<tbody>
<tr>
<td>To update section 1, 4.2, 4.4, 4.6, 4.8, 5.1 and 5.2 of the Summaries of Product Characteristics (SmPC) in line with the reference product, Solu-Medrone. As a consequence, the Patient Information Leaflet (PIL) has been updated.</td>
<td>UK/H/4085/001-002/IB/006</td>
<td>SmPC and PIL</td>
<td>08/03/2016</td>
<td>07/04/2016</td>
<td>Approved</td>
<td>Yes-see Annex 1</td>
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ANNEX 1

Our Reference: PL 18157/0227-0014  
PL 18157/0228-0016

Product: Methylprednisolone 500 mg powder and solvent for solution for injection/infusion

Methylprednisolone 1000 mg powder and solvent for solution for injection/infusion

Marketing Authorisation Holder: Beacon Pharmaceuticals Ltd
Active Ingredient(s): Methylprednisolone sodium succinate

Type of Procedure: Mutual recognition
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard
EU Procedure Number (if applicable): UK/H/4085/001-002/IB/006

Reason: To update section 1, 4.2, 4.4, 4.6, 4.8, 5.1 and 5.2 of the Summaries of Product Characteristics (SmPC) in line with the reference product, Solu-Medrone. As a consequence, the Patient Information Leaflet (PIL) has been updated.

Supporting Evidence
Revised SmPC fragments and PIL.

Evaluation
The proposed changes to the SmPCs, and PIL are in line with the reference product. The updated SmPC fragments, PIL have been incorporated into the Marketing Authorisations:

Conclusion
The proposed changes to the SmPCs and PIL are acceptable.

Decision - Approved on 07 April 2016.