Public Assessment Report

Decentralised Procedure

Dexamethasone 10 mg/5ml Oral Solution

(dexamethasone sodium phosphate)

Procedure No: UK/H/4489/001/DC

UK Licence No: PL 00427/0218

Rosemont Pharmaceuticals Limited
This is a summary of the Public Assessment Report (PAR) for Dexamethasone 10mg/5ml Oral Solution (PL 00427/0218; UK/H/4489/001/DC). It explains how Dexamethasone 10mg/5ml 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 Dexamethasone 10mg/5ml Oral Solution.

For practical information about using Dexamethasone 10mg/5ml Oral Solution, patients should read the package leaflet or contact their doctor or pharmacist.

**What is Dexamethasone 10mg/5ml Oral Solution and what is it used for?**
Dexamethasone 10mg/5ml Oral Solution is a medicine that contains the active substance dexamethasone (as dexamethasone sodium phosphate). Dexamethasone 10mg/5ml Oral Solution can be used in adults for:
- replacing natural corticosteroids when levels have been reduced
- treating swelling (inflammation) and certain allergies
- reducing swelling of the brain which is not caused by a head injury
- treating cancer
- controlling how well the adrenal glands work. These are glands that are next to the kidneys
- treating a number of different diseases of the immune system.

This medicine may be prescribed for a condition different from those listed above; if so, patients should ask their doctor why this medicine has been prescribed.

Dexamethasone 10mg/5ml Oral Solution is a ‘generic’ medicine. This means that Dexamethasone 10mg/5ml Oral Solution is similar to a reference medicine already authorised in the European Union (EU) called Dexamethasone Tablets BP 2mg (PL 00065/5045R ;Organon Laboratories Limited, UK).

**How is Dexamethasone 10mg/5ml Oral Solution used?**
Dexamethasone 10mg/5ml Oral Solution is taken by mouth.

Dexamethasone 10mg/5ml Oral Solution can only be obtained on prescription.

**How does Dexamethasone 10mg/5ml Oral Solution work?**
The active substance, dexamethasone (as dexamethasone sodium phosphate), belongs to a group of medicines called corticosteroids. Corticosteroids are hormones that are found naturally in the body that help to keep the body healthy and well. Boosting the body with extra corticosteroid, such as Dexamethasone 10mg/5ml Oral Solution, is an effective way to treat various illnesses involving inflammation in the body. Dexamethasone lowers inflammation, which could otherwise go on making certain conditions worse. Dexamethasone 10mg/5ml Oral Solution must be taken regularly to get maximum benefit from it.

**How has Dexamethasone 10mg/5ml Oral Solution been studied?**
Because Dexamethasone 10mg/5ml Oral Solution is a generic medicine, studies in patients have been limited to tests to determine that it is similar to the reference medicine, Dexamethasone Tablets BP 2mg (Organon Laboratories Limited, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

In addition, the company (Rosemont Pharmaceuticals Limited) provided data from the published literature on dexamethasone.
What are the benefits and risks of Dexamethasone 10mg/5ml Oral Solution?
Because Dexamethasone 10mg/5ml Oral Solution is a generic medicine that is bioequivalent to the reference medicine, its benefits and risks are taken as being the same as those of the reference medicine.

Why is Dexamethasone 10mg/5ml Oral Solution approved?
It was concluded that, in accordance with EU requirements, Dexamethasone 10mg/5ml Oral Solution has been shown to have comparable quality and to be bioequivalent to Dexamethasone Tablets BP 2mg (Organon Laboratories Limited, UK). Therefore, the view was that, as for Dexamethasone Tablets BP 2mg (Organon Laboratories Limited, UK), the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Dexamethasone 10mg/5ml Oral Solution?
A risk management plan has been developed to ensure that Dexamethasone 10mg/5ml Oral Solution 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 Dexamethasone 10mg/5ml Oral Solution, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Dexamethasone 10mg/5ml Oral Solution.
A Marketing Authorisation was granted in the UK on 24 October 2013.

The full PAR for Dexamethasone 10mg/5ml Oral Solution follows this summary.

For more information about treatment with Dexamethasone 10mg/5ml Oral Solution, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in 12-2013.
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**Module 1**

**Information about the initial procedure**

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Dexamethasone 10mg/5ml Oral Solution</th>
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<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10</td>
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<tr>
<td><strong>Active Substance</strong></td>
<td>Dexamethasone sodium phosphate</td>
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<tr>
<td><strong>Form</strong></td>
<td>Oral solution</td>
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<tr>
<td><strong>Strength</strong></td>
<td>10mg/5ml (dexamethasone [as dexamethasone sodium phosphate])</td>
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| **MA Holder** | Rosemont Pharmaceuticals Ltd  
Rosemont House  
Yorkdale Industrial Park  
Braithwaite Street  
Leeds  
LS11 9XE  
UK |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | Greece, Ireland, Malta and Sweden |
| **Procedure Number** | UK/H/4489/001/DC |
| **Timetable** | Day 210 – 07 October 2013 |
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Dexamethasone 10mg/5ml Oral Solution (PL 00427/0218; UK/H/4489/001/DC) could be approved. The product is a prescription-only medicine (POM).

Dexamethasone 10mg/5ml Oral Solution contains the active ingredient, dexamethasone (as dexamethasone sodium phosphate), which is a synthetic adrenocorticosteroid with glucocorticoid activity and is about 25-30 times more potent than hydrocortisone. It has anti-inflammatory and immunosuppressive activity and is indicated in a wide range of conditions where symptomatic antiinflammatory/immunosuppressive therapy is required. Dexamethasone 10mg/5ml Oral Solution is designed for use in certain endocrine and non-endocrine disorders, in certain cases of cerebral oedema and for diagnostic testing of adrenocortical hyperfunction as detailed below:

Endocrine disorders:
Endocrine exophthalmos.

Non-endocrine disorders:
Dexamethasone may be used in the treatment of non-endocrine corticosteroid responsive conditions including:

- **Allergy and anaphylaxis**: Anaphylaxis.
- **Arteritis collagenosis**: Polymyalgia rheumatica, polyarteritis nodosa.
- **Haematological disorders**: Haemolytic anaemia (also auto immune), leukaemia, myeloma, idiopathic thrombocytopenic purpura in adults, reticulolymphoproliferative disorders (see also under oncological disorders).
- **Gastroenterological disorders**: For treatment during the critical stage in: ulcerative colitis (rectal only); regional enteritis (Crohn’s disease), certain forms of hepatitis.
- **Muscular disorders**: Polymyositis.
- **Neurological disorders**: Raised intra-cranial pressure secondary to cerebral tumours, acute exacerbations of multiple sclerosis.
- **Ocular disorders**: Anterior and posterior uveitis, optic neuritis, chorioretinitis, iridocyclitis, temporal arthritis, orbital pseudotumour.
- **Renal disorders**: Nephrotic syndrome.
- **Pulmonary disorders**: Chronic bronchial asthma, aspiration pneumonitis, chronic obstructive pulmonary disease (COPD), sarcoidosis, allergic pulmonary disease such as farmer’s and pigeon breeder’s lung, Löffler’s syndrome, cryptogenic fibrosing alveolitis.
- **Rheumatic disorders**: some cases or specific forms (Felty’s syndrome, Sjögren’s syndrome) of rheumatoid arthritis, including juvenile rheumatoid arthritis, acute rheumatism, lupus erythematosus disseminatus, temporal arteritis (polymyalgia rheumatica).
- **Skin disorders**: Pemphigus vulgaris, bullous pemphigoid, erythrodermas, serious forms of erythema multiforme (Stevens-Johnson syndrome), mycosis fungoides, bullous dermatitis herpetiformis.
- **Oncological Disorders**: lymphatic leukaemia, especially acute forms, malignant lymphoma (Hodgkin’s disease, non-Hodgkin’s lymphoma), metastasized breast cancer, hypercalcaemia as a result of bone metastasis or Kahler’s disease, Kahler’s disease.
- **Various**: intense allergic reactions; as immunosuppressant in organ transplantation; as an adjuvant in the prevention of nausea and vomiting and in the treatment of cancer with oncolytics that have a serious emetic effect.
The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Greece, Ireland, Malta and Sweden as Concerned Member States (CMS). The application was submitted under Article 10 of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Dexamethasone Tablets BP 2mg (PL 00065/5045R; Organon Laboratories Limited, UK), which was first authorised in the UK on 29 March 1990.

A single-dose bioequivalence study was submitted to support this application, comparing the applicant’s test product Dexamethasone 10mg/5ml Oral Solution (1x5ml) and the reference product (x 5) Dexamethasone Tablets BP 2mg (Organon Laboratories Limited, UK), under fasting conditions. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical efficacy studies were performed for this application, 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.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. 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 and CMS considered that the application could be approved at the end of procedure (Day 210) on 07 October 2013. After a subsequent national phase, a licence was granted in the UK on 24 October 2013.

II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Dexamethasone 10mg/5ml Oral Solution |
| Name(s) of the active substance(s) (INN) | Dexamethasone sodium phosphate |
| Pharmacotherapeutic classification (ATC code) | Corticosteroid (ATC code: H02A B02) |
| Pharmaceutical form and strength | Oral solution; 10mg/5ml (Each 5ml contains 10mg dexamethasone (as dexamethasone sodium phosphate)) |
| Reference number for the Decentralised Procedure | UK/H/4489/001/DC |
| Reference Member State (RMS) | United Kingdom |
| Concerned Member States (CMS) | Greece, Ireland, Malta and Sweden |
| Marketing Authorisation Number | PL 00427/0218 |
| Name and address of the authorisation holder | Rosemont Pharmaceuticals Ltd Rosemont House Yorkdale Industrial Park Braithwaite Street Leeds LS11 9XE UK |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Dexamethasone sodium phosphate
Chemical Name: 9-fluoro-11ß, 17, 21-trihydroxy-16-methylpregna-1,4-diene-3, 20-dione disodium 21-phosphate
Molecular formula: C_{22}H_{28}FNa_{2}O_{8}P

Molecular mass: 516.4
Appearance: A white or almost white powder
Solubility: Freely soluble in water, slightly soluble in alcohol and practically insoluble in ether and methylene chloride.

Dexamethasone sodium phosphate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, dexamethasone sodium phosphate, are either covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

MEDICINAL PRODUCT

Other Ingredients
Other ingredients consist of the pharmaceutical excipients propylene glycol (E1250), benzoic acid (E210), citric acid monohydrate (E330), sodium citrate (E331), liquid maltitol (E965), sorbitol liquid (non crystallising) (E420) and purified water. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Certificates of Analysis have been provided for all excipients, showing compliance with their respective specifications.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, stable, oral solution containing dexamethasone (as dexamethasone sodium phosphate) 10mg/5ml, to complement the applicant’s authorised product, Dexamethasone 2mg/5ml Oral Solution.

Suitable pharmaceutical development data have been provided for this application.

Comparative in-vitro dissolution profiles have been provided for this product and the reference product.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full production-scale batches that have shown satisfactory results.
Control of Finished Product
The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data have been provided, which comply with the release specification. Certificates of Analysis have been provided for all working reference standards used.

Container-Closure System
The finished product is packaged in amber Type III glass bottles with high-density polyethylene, (HDPE), expanded polyethylene (EPE) wadded, child resistant closures and low-density polyethylene (LDPE) bottle adaptors.

A dosing device, consisting of a polypropylene (PP) body and a purple HDPE plunger with a capacity of 5ml and dosage graduation at every 0.25ml, is provided with the product.

The product is available in pack sizes of 30ml and 150ml.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards that comply with guidance concerning materials in contact with foodstuff.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 17 months has been approved for the unopened product and 1 month for the opened product, with the storage instructions ‘Do not store above 25°C. Do not refrigerate or freeze. Store in the original package in order to protect from light.’

Once opened, the product should be used within 1 month; any unused solution should be discarded.

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

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section III.3, Clinical Aspects.

Summary of Product Characteristics (SmPC), Product Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are satisfactory from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. 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 leaflet contains.

Marketing Authorisation Application (MAA) Form
The MAA form is satisfactory from a pharmaceutical perspective.
Expert Report (Quality Overall Summary)
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of dexamethasone are well-known, no new non-clinical data have been submitted and none are required.

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.

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

The grant of a Marketing Authorisation is recommended.

III.3 CLINICAL ASPECTS
Clinical Pharmacology
The clinical pharmacology of dexamethasone is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required for this application.

In support of the application, the Marketing Authorisation Holder submitted the following bioequivalence study:

A single-dose, randomized, open-label, two-period, two-sequence, two-treatment, crossover, comparative bioavailability study of Dexamethasone 10mg/5ml (as dexamethasone sodium phosphate) Oral Solution (Rosemont Pharmaceuticals Limited, UK) and Dexamethasone Tablets BP 2mg (Organon Pharmaceuticals Limited, UK) in healthy male and female subjects under fasting conditions.

The subjects were administered a single dose of either the test (Treatment A; 1x5 ml (10 mg/5ml)) or the reference (Test B; 5 x 2 mg) product with 240 ml of water, after at least a 10-hour overnight fast. The subjects were randomly assigned to receive the study test and reference products according to one of the two dosing sequences A-B or B-A. Blood samples were collected pre-dose and up to 48 hours after each administration. The washout period between the treatment arms was 7 days. The pharmacokinetic results are presented below:
Pharmacokinetic parameters (treatment A (test)/ Treatment B (reference) ratios of geometric means, confidence intervals [CI] and the intra-subject variability for AUC and $C_{\text{max}}$ for dexamethasone)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ratio of Geometric Means</th>
<th>90% Confidence Interval</th>
<th>Intrasubject CV (%)</th>
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<tr>
<td>$AUC_{0-t}$ (ng·h/mL)</td>
<td>98.45</td>
<td>89.64 - 108.13</td>
<td>12.84</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (ng·h/mL)</td>
<td>97.93</td>
<td>88.37 – 108.52</td>
<td>14.08</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>101.86</td>
<td>90.38 – 114.79</td>
<td>16.41</td>
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</tbody>
</table>

$AUC_{0-t}$: area under the plasma concentration-time curve from time zero to $t$ hours

$AUC_{0-\infty}$: area under the plasma concentration-time curve from time zero to infinity

$C_{\text{max}}$: maximum plasma concentration

Ratios and 90% CI calculated from ln-transformed data

The *Guidance on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1) defines the 90% confidence limits as 80.00% to 125.00% for $C_{\text{max}}$ and AUC values. The 90% confidence intervals of the test/reference ratio for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{\text{max}}$ lie within the acceptable limits. Thus, the data support the claim that the applicant’s test product (1 x 5ml) Dexamethasone 10mg/5ml is bioequivalent to the reference product (x 5) Dexamethasone Tablets BP 2mg (Organon Pharmaceuticals Limited, UK) under fasting conditions.

**Efficacy**

The efficacy of dexamethasone is well-known. No new efficacy data have been submitted and none are required for an application of this type.

**Safety**

With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues arose during the bioequivalence study.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

The SmPC, PIL and labels are acceptable from a clinical perspective. The PIL is consistent with the details in the SmPC and in line with the current guidance. The labelling is in line with the current guidance.

**Clinical Expert Report (Clinical Overview)**

The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Pharmacovigilance System and Risk Management Plan**

The Pharmacovigilance System, as described by the Marketing Authorisation Holder (MAH), fulfils the requirements and provides adequate evidence that the MAH 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.

An acceptable Risk Management Plan has been provided for this application.

**Conclusion**

The grant of a Marketing Authorisation is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Dexamethasone 10mg/5ml Oral Solution 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. As the pharmacokinetics, pharmacodynamics and toxicology of dexamethasone are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for this type of application.

Bioequivalence has been demonstrated between the applicant’s test product (1 x 5ml) and the reference product (x 5 Dexamethasone Tablets BP 2mg; Organon Pharmaceuticals Limited, UK).

SAFETY
With the exception of the safety data generated from the bioequivalence study, no new data were submitted and none are required for this type of application. As the safety profile of dexamethasone is well known, no additional safety data were required. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate and in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with dexamethasone is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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