Dexamethasone 2 mg/5 ml Oral Solution
(dexamethasone sodium phosphate)

PL 17507/0197

UKPAR

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Lay Summary

Dexamethasone 2 mg/5ml Oral Solution
(dexamethasone sodium phosphate, oral solution, 2 mg/5ml)

This is a summary of the Public Assessment Report (PAR) for Dexamethasone 2 mg/5 ml Oral Solution (PL 17507/0197). It explains how Dexamethasone 2 mg/5 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 Dexamethasone 2 mg/5 ml Oral Solution.

For practical information about using Dexamethasone 2 mg/5 ml Oral Solution, patients should read the package leaflet or contact their doctor or pharmacist.

What is Dexamethasone 2 mg/5 ml Oral Solution and what is it used for?
Dexamethasone 2 mg/5 ml Oral Solution contains the active substance, dexamethasone (as dexamethasone sodium phosphate). Dexamethasone belongs to a group of medicines called corticosteroids.

This medicine can be used for:
- replacing natural corticosteroids when levels have been reduced;
- reducing swelling of the brain which is not caused by a head injury;
- treating swelling (inflammation) and certain allergies;
- treating cancer;
- controlling how well your adrenal glands work. These are glands that are next to your kidneys;
- croup in babies and children. This affects the windpipe and the two airways that branch off from it to the lungs. The top of the airway is slightly blocked causing the barking cough, hoarse voice, a harsh sound (known as ‘stridor’) and breathing difficulties.

Dexamethasone 2 mg/5 ml Oral Solution is a ‘generic’ medicine. This means that Dexamethasone 2 mg/5 ml 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 2 mg/5 ml Oral Solution used?
Dexamethasone 2mg/5 ml Oral Solution can only be obtained on prescription.

Dexamethasone 2 mg/5ml Oral Solution is taken by mouth. The prescribing doctor will advise as to how to take this medicine.

For further information on how Dexamethasone 2 mg/5 ml Oral Solution is used, please refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

How does Dexamethasone 2 mg/5 ml Oral Solution work?
Dexamethasone, the active substance, 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, is an effective way to treat various illnesses involving inflammation in the body. Dexamethasone lowers inflammation, which could otherwise go on making some conditions worse.
How has Dexamethasone 2 mg/5 ml Oral Solution been studied?
As Dexamethasone 2 mg/5 ml 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 considered to be bioequivalent when they produce the same levels of the active substance in the body.

In addition, the company (Auden McKenzie (Pharma Division) Limited) provided data from the published literature on dexamethasone.

What are the benefits and risks of Dexamethasone 2 mg/5 ml Oral Solution?
Because Dexamethasone 2 mg/5 ml 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 2 mg/5 ml Oral Solution approved?
It was concluded that, in accordance with EU requirements, Dexamethasone 2 mg/5 ml 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 benefits outweighs the identified risks.

What measures are being taken to ensure the safe and effective use of Dexamethasone 2 mg/5ml Oral Solution?
Safety information has been included in the Summary of Product Characteristics and the package leaflet for Dexamethasone 2 mg/5 ml Oral Solution, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Dexamethasone 2 mg/5 ml Oral Solution.
A Marketing Authorisation was granted in the UK on 02 May 2014.

The full PAR for Dexamethasone 2 mg/5 ml Oral Solution follows this summary.

For more information about treatment with Dexamethasone 2 mg/5 ml Oral Solution, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in June 2014.
Dexamethasone 2 mg/5 ml Oral Solution
(dexamethasone sodium phosphate)

PL 17507/0197

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Auden McKenzie (Pharma Division) Limited a Marketing Authorisation for the medicinal product Dexamethasone 2 mg/5 ml Oral Solution (PL 17507/0197) on 02 May 2014. The product is a prescription-only medicine (POM).

Dexamethasone 2 mg/5ml Oral Solution contains the active ingredient, dexamethasone (as dexamethasone sodium phosphate), which is a highly potent, long-acting, synthetic glucocorticoid with negligible sodium retaining properties. Its anti-inflammatory potency is 7 times greater than prednisolone and like other glucocorticoids, dexamethasone also has anti-allergic, antipyretic and immunosuppressive properties. Dexamethasone 2 mg/5 ml 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 collagenesis: polymyalgia rheumatica and polyarteritis nodosa;
- Haematological disorders: haemolytic anaemia (also auto immune), leukaemia, myeloma, idiopathic thrombocytopenic purpura in adults and 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) and certain forms of hepatitis;
- Muscular disorders: polymyositis;
- Neurological disorders: raised intra-craniol pressure secondary to cerebral tumours and acute exacerbations of multiple sclerosis;
- Ocular disorders: anterior and posterior uveitis, optic neuritis, chorioretinitis, iridocyclitis, temporal arteritis and orbital pseudotumour;
- Renal disorders: nephrotic syndrome;
- Pulmonary disorders: chronic bronchial asthma, aspiration pneumonia, chronic obstructive pulmonary disease (COPD), sarcoidosis, allergic pulmonary disease such as farmer’s and pigeon breeder’s lung, Löeffler’s syndrome and 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 and temporal arteritis (polymyalgia rheumatica);
- Skin disorders: pemphigus vulgaris, bullous pemphigoid, erythrodermas, serious forms of erythema multiforme (Stevens-Johnson syndrome), mycosis fungoides and 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 and 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;
- Childhood croup: heterogeneous group of illnesses affecting the larynx, trachea and bronchi. Laryngotracheitis, laryngotracheobronchitis, laryngotracheobronchopneumonitis and spasmodic croup are included in the croup syndrome.
The application was submitted under Article 10(1) 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 (1 x 5 ml) Dexamethasone 2 mg/5 ml Oral Solution and the reference product (x 1) 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.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Dexamethasone 2 mg/5 ml Oral Solution outweigh the risks and a Marketing Authorisation was granted.
PHARMACEUTICAL ASSESSMENT

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: \( \text{C}_{22}\text{H}_{28}\text{FNa}_2\text{O}_8\text{P} \)
Structure:

Molecular mass: 516.4
Appearance: A white or almost white, very hygroscopic 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 covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients benzoic acid (E210), propylene glycol (E1520), citric acid monohydrate (E330), liquid maltitol (E965), garden mint flavour (containing isopropanol and propylene glycol), liquid sorbitol (non-crystallising) (E420), sodium citrate (E331), and purified water. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of garden mint flavour, which complies with a suitable in-house specification.

Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

None of the excipients contains material 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 2 mg/5 ml dexamethasone (as dexamethasone sodium phosphate) comparable in performance to the reference product, Dexamethasone Tablets BP 2 mg (Organon Laboratories Limited).

Suitable pharmaceutical development data have been provided for this application.

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 pilot-scale batches and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on future full-scale production batches.

**Control of Finished Product**  
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided, which comply with the release specifications.

**Container Closure System**  
The product is packaged in pharmaceutical grade Type III amber glass bottles with polypropylene, polyethylene, tamper evident, child resistant closures, in a pack size of 150 ml.

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.

**Stability of the product**  
Finished 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 2 years for the unopened product and 3 months for the opened product, with no special storage conditions.

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

**Bioequivalence**  
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**  
The SmPC, PIL and labelling are satisfactory from a pharmaceutical perspective.

**MAA (Marketing Authorisation Application) Form**  
The MAA form is satisfactory from a pharmaceutical perspective.

**Expert Report (Quality Overall Summary)**  
The quality overall summary is 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.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
As the pharmacodynamic, pharmacokinetic and toxicological properties of dexamethasone are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT (NON-CLINICAL OVERVIEW)
The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

ENVIRONMENTAL RISK ASSESSMENT
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.

CONCLUSION
The grant of Marketing Authorisation is recommended.
CLINICAL ASSESSMENT

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 2 mg/5 ml (as dexamethasone sodium phosphate) Oral Solution (Auden McKenzie ([Pharma Division], UK) and Dexamethasone BP 2 mg Tablets (Organon Pharmaceuticals Limited, UK) in healthy male subjects under fasting conditions.

The subjects were administered a single dose of either the test (Treatment A; 1x5 ml [2 mg/5ml]) or the reference (Treatment B; 2 mg) product with 240 ml of water, after at least a 10-hour overnight fast. Blood samples were collected pre-dose and up to 24 hours after each administration. The washout period between the treatment arms was 7 days. The pharmacokinetic results are presented below:

Table - A: Descriptive Statistics of Formulation Means for Dexamethasone obtained by a Non-Compartmental Model

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters (Units)</th>
<th>Mean ± SD* (Un-transformed data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ mL)</td>
<td>32.46 ± 8.97</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.h/ mL)</td>
<td>165.51 ± 52.03</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng.h/ mL)</td>
<td>175.51 ± 61.72</td>
</tr>
</tbody>
</table>

* All figures are rounded to two decimal places.

AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours
AUC<sub>0-∞</sub> area under the plasma concentration-time curve from time zero to infinity
C<sub>max</sub> maximum plasma concentration

Table - B: Geometric Least Squares Mean, Ratios and 96.7% Confidence Intervals for Pharmacokinetic Parameters (C<sub>max</sub> and AUC<sub>0-t</sub>) of Dexamethasone

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters (Units)</th>
<th>Ln-transformed</th>
<th>96.7% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Geometric Least Squares Mean*</td>
<td>Lower</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ mL)</td>
<td>Test Product(T)</td>
<td>Reference Product(R)</td>
</tr>
<tr>
<td></td>
<td>31.52</td>
<td>35.19</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.h/ mL)</td>
<td>Test Product(T)</td>
<td>Reference Product(R)</td>
</tr>
<tr>
<td></td>
<td>158.67</td>
<td>180.53</td>
</tr>
</tbody>
</table>

* All figures are rounded to two decimal places.

AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours
C<sub>max</sub> maximum plasma concentration

Ratios and 96.7% Confidence Intervals are calculated from ln-transformed data
Conclusion of Bioequivalence study
The Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**) defines the 90% confidence limits as 80.00% to 125.00% for \( C_{\text{max}} \) and AUC values. The 96.7% confidence intervals of the test/reference ratio for \( \text{AUC}_{0-t} \) and \( C_{\text{max}} \) lie within the acceptable limits of 80.00% to 125%. The applicant has provided suitable justification for the use of the adjusted confidence interval 96.7% instead of a confidence limit 90%. Thus, the data support the claim that the applicant’s test product (1 x 5 ml) Dexamethasone 2 mg/5ml is bioequivalent to the reference product (x 1) Dexamethasone BP 2 mg Tablets (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.

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.

Suitable justification has been provided for non-submission of a Risk Management Plan (RMP) for this application which was received prior to 21 July 2012, the date from which pharmacovigilance regulations in accordance with Directive 2010/84/EU came into force. As the hybrid applications are for substitution of an already authorised product, for which safety concerns requiring additional risk minimisation have not been identified, there is no need for a detailed European Risk Management Plan and the routine pharmacovigilance activities are sufficient. The reference product has been in use for many years and the safety profiles of the active ingredients are well-established.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPC, PIL and labelling are acceptable from a clinical perspective. The SmPC is consistent with that for the reference product. The PIL text is consistent with the details in the SmPC and in line with current guidance. The labelling is also in line with current guidance.

CLINICAL EXPERT REPORT (CLINICAL OVERVIEW)
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

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

QUALITY
The important quality characteristics of Dexamethasone 2 mg/5 ml 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 and none is required for this type of application. 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 5 ml) and the reference product Dexamethasone Tablets BP 2mg (x 1; 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.
Dexamethasone 2 mg/5ml Oral Solution
(dexamethasone sodium phosphate)

PL 17507/0197

**STEPS TAKEN FOR ASSESSMENT**

1. The MHRA received the Marketing Authorisation application on 07 October 2011.

2. Following standard checks and communication with the applicant the MHRA considered the application valid on 17 October 2011.

3. Following assessment of the application, the MHRA requested further information relating to the dossier on 24 January 2012 and 28 June 2013.

4. The applicant responded to the MHRA’s requests, providing further information on the dossier on 30 January 2013 and 20 August 2013.

5. The application was granted on 02 May 2014.
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.
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.