Public Assessment Report

Decentralised Procedure

DEXAMETHASONE 2MG/5ML ORAL SOLUTION

(Dexamethasone sodium phosphate)

Procedure No: UK/H/5139/001/DC

UK Licence No: PL 20046/0260

FOCUS PHARMACEUTICALS LTD
LAY SUMMARY

On 29 January 2013, Cyprus, Greece and the UK agreed to grant a Marketing Authorisation to Focus Pharmaceuticals Ltd for the medicinal product Dexamethasone 2mg/5ml Oral Solution (PL 20046/0260; UK/H/5139/001/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, a Marketing Authorisation was granted in the UK on 07 March 2013. This product is a prescription-only medicine (POM).

Dexamethasone 2mg/5ml Oral Solution contains the active ingredient dexamethasone sodium phosphate. Dexamethasone sodium phosphate belongs to a group of medicines called steroids (the full name is corticosteroids). Corticosteroids occur naturally in the body, and help to maintain health and well-being. Boosting your body with extra corticosteroid (such as dexamethasone) is an effective way to treat various illnesses involving inflammation in the body.

Dexamethasone 2mg/5ml Oral Solution reduces this inflammation, which could otherwise go on making your condition worse. You must take this medicine regularly to get maximum benefit from it.

Dexamethasone 2mg/5ml Oral Solution is used for one of the following:

- where your natural corticosteroid levels have been reduced and you need to replace them
- where swelling of the brain has occurred
- if you are having tests for diseases which may decrease your natural corticosteroid level, such as Cushing’s syndrome (a hormonal disorder)
- to reduce inflammation and suppress the immune system in:
  - allergy (hypersensitivity)
  - polymyalgia rheumatica (chronic inflammation of the larger arteries), polyarteritis nodosa (chronic inflammation of small and medium arteries)
  - blood disorders including haemolytic anaemia (disorder which breaks down red blood cells), leukaemia (cancer of the blood), myeloma (bone marrow tumour)
  - Crohn’s disease, ulcerative colitis (inflammation of the bowel), hepatitis
  - polymyositis (inflammation of muscles)
  - increased pressure in the head not linked to tumours, worsening of multiple sclerosis
  - inflammation of the eye
  - inflammation of the kidney
  - breathing problems including chronic bronchial asthma and chronic obstructive pulmonary disease (COPD) which may show as shortness of breath during exercise, difficulty breathing in and out deeply and persistent cough. Disorders where there is inflammation of the lung.
  - rheumatoid arthritis (painful joint disease), rheumatism, inflammation of a wide area of the body
  - chronic and severe diseases of the skin (including Stevens-Johnson syndrome and a rare condition known as mycosis fungoides)
  - leukaemia of the lymphatic system, Hodgkin’s and Non-Hodgkin’s lymphoma, breast cancer that has spread around the body, Kahler’s disease (cancer of blood cells) and high calcium levels caused by this disease
o after organ transplants and to prevent nausea and vomiting following chemotherapy

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Dexamethasone 2mg/5ml Oral Solution outweigh the risks and a Marketing Authorisation has been granted.
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# Module 1

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<tr>
<th><strong>Product Name</strong></th>
<th>Dexamethasone 2mg/5ml Oral Solution</th>
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<tr>
<td><strong>Type of Application</strong></td>
<td>Article 10(a), well-established use</td>
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<td><strong>Active Substance</strong></td>
<td>Dexamethasone sodium phosphate</td>
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<td><strong>Form</strong></td>
<td>Oral solution</td>
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<td><strong>Strength</strong></td>
<td>2mg/5ml</td>
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<td><strong>MA Holder</strong></td>
<td>Focus Pharmaceuticals Ltd</td>
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<td>Unit 5, Faraday Court</td>
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<td><strong>Concerned Member State (CMS)</strong></td>
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<td><strong>Timetable</strong></td>
<td>Day 210 – 29 January 2013</td>
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Module 2
Summary of Product Characteristics

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.
Module 3
Patient Information Leaflet (PIL)

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.
Module 4
Labelling

Carton:

Dexamethasone 2mg/5ml Oral Solution

Each ml of solution contains 0.4 mg of dexamethasone (as dexamethasone sodium phosphate).

Excipients:
Propylene glycol (E1520), Liquid maltitol (E965), Liquid sorbitol (non-crystalline, E420), benzoic acid, See leaflet for full information.

Read the package leaflet before use.

Oral use.

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use the product if solid particles are observed inside the solution.

Do not store above 25°C.

Do not refrigerate.

Use within 3 months of opening.

PL 25048/0256
MA Holder:
Fisons Pharmaceuticals Ltd.
Unit 5, Parley Court,
Burton upon Trent,
DE14 2XW, UK.

41100211/0

"CUTTER AMENDED TO NEW SIZE AT V3 - NOT MANUFACTURER'S CUTTER"

Marburg Medium Braille Font 28.3465pt / Leading 28.3465pt

Dexamethasone
2mg/5ml
Oral Solution
Bottle label:
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 2mg/5ml Oral Solution (PL 20046/0260; UK/H/5139/001/DC) could be approved. This application was submitted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Cyprus and Greece as Concerned Member States (CMS). This product is a prescription-only medicine (POM).

Dexamethasone is a corticosteroid. It 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 arteritis, 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, Löfler'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.

Dexamethasone is a highly potent and long-acting glucocorticoid with negligible sodium retaining properties and is therefore, particularly suitable for the use in patients with cardiac failure and hypertension. Its anti-inflammatory potency is 7 times greater than prednisolone and, like other glucocorticoids, dexamethasone also has anti-allergic, antipyretic and immunosuppressive properties.

This application was submitted according to Article 10(a) of Directive 2001/83/EC, as amended, claiming to be an application for a product containing active substances of well-established use.

No new non-clinical or clinical studies were conducted for this application, which is acceptable given that this is a bibliographic application for a product containing an active of well-established use.

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 products.

The RMS and CMS considered that the application could be approved with the end of procedure (Day 210) on 29 January 2013. After a subsequent national phase, the licence was granted in the UK on 07 March 2013.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Dexamethasone 2mg/5ml Oral Solution</th>
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<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Dexamethasone sodium phosphate</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Glucocorticoids (ATC code: H02AB02)</td>
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<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Oral solution, 2mg/5ml</td>
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<tr>
<td>Reference numbers for the Decentralised procedure</td>
<td>UK/H/5139/001/DC</td>
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<td>United Kingdom</td>
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<td>Marketing Authorisation Number(s)</td>
<td>PL 20046/0260</td>
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<tr>
<td>Name and address of the authorisation holder</td>
<td>Focus Pharmaceuticals Ltd</td>
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III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Dexamethasone sodium phosphate

Chemical name: 9-Fluoro-11ß,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl disodium phosphate.

Structure:

Appearance: Dexamethasone sodium phosphate is a white or almost white powder.

Solubility: Dexamethasone sodium phosphate is freely soluble in water, slightly soluble in ethanol (96%) and practically insoluble in 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 (EDQM) Certificate of Suitability.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients benzoic acid (E210), propylene glycol (E1520), citric acid monohydrate (E330), liquid maltitol (E965), liquid sorbitol (non-crystallising) (E420), sodium citrate dihydrate (E331), mint flavour and purified water.

All excipients used comply with their respective European Pharmacopoeia monograph, with the exception of mint flavour which is compliant with a suitable in-house specification and is in compliance with Council Directive 88/388/EEC on flavourings for use in foodstuff. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.
**Pharmaceutical Development**

The objective of the development programme was to produce an oral solution containing dexamethasone (as sodium phosphate) 2mg/5ml that is qualitatively and quantitatively similar and pharmaceutically equivalent to the medicinal product Dexamethasone Rosemont 2 mg/5ml oral solution (Rosemont Pharmaceuticals Ltd, UK).

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 at commercial scale and has shown satisfactory results.

**Finished Product Specification**

The proposed finished product specification is 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.

**Container-Closure System**

The finished product is packaged in amber (Type III) glass bottles, with child-resistant, tamper-evident screw caps in pack sizes of 150ml.

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

**Stability of the product**

Stability studies were performed in accordance with current guidelines on batches of the 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 which reduces to 3 months after first opening with the storage conditions ‘Do not store above 25°C. Do not refrigerate. The storage at temperatures higher than 25°C could lead to precipitation inside the solution. Do not use the product if solid particles are observed inside the solution.’

**Bioequivalence/bioavailability**

No bioequivalence studies have been submitted and none are required to support an application of this type.

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

The SmPC, PIL and labels are acceptable.

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 leaflet conforms to the requirements. The test shows that the patients/users are able to act upon the information that the leaflet contains.

**MAA (Marketing Authorisation Application) forms**

The MAA form is satisfactory.
Expert report (Quality Overall Summary)
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical view-point.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of dexamethasone sodium phosphate 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.

Since Dexamethasone 2mg/5ml Oral Solution is intended for substitution of the existing market for this product type, this will not lead to an increased exposure to the environment. An environmental risk assessment (ERA) is therefore not deemed necessary.

There are no objections to the approval of this product from a non-clinical view-point.

III.3 CLINICAL ASPECTS
The clinical pharmacology of dexamethasone sodium phosphate is well known. No new pharmacodynamic or pharmacokinetic data are provided or required for this application.

Efficacy
No new efficacy data were submitted and none were required for this application.

Safety
No new safety data were submitted and none were required for this application. The applicant has provided an acceptable safety review from the literature. No new safety issues have been raised from this application.

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

Clinical Expert Report (Clinical Overview)
The clinical expert report 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 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 not submitting a risk management plan for this application.
Conclusion
There are no objections to the approval of this application from a clinical view-point.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Dexamethasone 2mg/5ml Oral Solution for Injection 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 were required for an application of this type. A non-clinical overview has been provided by an appropriately qualified person and consists of a review of the published literature.

EFFICACY
No new data were submitted and none were required for this type of application.

The efficacy of the active is well described and no new studies have been conducted. The applicant has summarised the current state of knowledge in their literature review.

SAFETY
The safety profiles of dexamethasone sodium phosphate are well-known. The literature review identified no new or unexpected safety issues or concerns.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory 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. Dexamethasone sodium phosphate is a well-known active substance. Extensive clinical experience with dexamethasone sodium phosphate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ratio is therefore considered to be positive.
# Module 6

## STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Date submitted</th>
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<th>Scope</th>
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