Public Assessment Report

Decentralised Procedure

DEXAMETHASONE 10MG/5ML ORAL SOLUTION
DEXAMETHASONE 20MG/5ML ORAL SOLUTION

(dexamethasone sodium phosphate)

Procedure No: UK/H/5437/001-2/DC

UK Licence No: PL 20046/0276 and PL 20046/0277

Focus Pharmaceuticals Ltd
LAY SUMMARY
Dexamethasone 10mg/5ml Oral Solution
Dexamethasone 20mg/5ml Oral Solution
(dexamethasone sodium phosphate)

This is a summary of the public assessment report (PAR) for Dexamethasone 10mg/5ml Oral Solution (PL 2004/0277; UK/H/5437/001/DC) and Dexamethasone 20mg/5ml Oral Solution (PL 2004/0276; UK/H/5437/002/DC). It explains how Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution were assessed and their authorisations recommended as well as their conditions of use. It is not intended to provide practical advice on how to use Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution.

For practical information about using Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution, patients should read the package leaflets or contact their doctor or pharmacist.

What are Dexamethasone 10mg/5ml and 20mg/5ml Oral Solutions and what are they used for?

Dexamethasone 10mg/5ml and 20mg/5ml Oral Solutions are medicines with ‘well-established use’. This means that the medicinal use of the active substance dexamethasone sodium phosphate is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution is used for one of the following:

- Where the natural corticosteroid levels have been reduced and they need to be replaced
- Reducing swelling on the brain which is not caused by a head injury
- If tests are being conducted for diseases which may decrease the 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 and 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 in 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)
  o 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

These medicines may be prescribed for a different condition from those listed above. If patients are unsure, they should ask their doctor why this medicine has been prescribed.

**How do Dexamethasone 10mg/5ml and 20mg/5ml Oral Solutions work?**

Dexamethasone belongs to a group of medicines called corticosteroids (steroids). Corticosteroids are hormones that occur naturally in the body, and help to maintain health and well-being. Boosting the body with extra corticosteroids (such as dexamethasone) is an effective way to treat various illnesses involving inflammation in the body. Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution reduces inflammation, which could otherwise make a condition worse. This medicine needs to be taken regularly in order to get maximum benefits.

**How are Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution used?**

Dexamethasone 10mg/5ml and 20mg/5ml Oral Solutions are taken by mouth. The doctor will prescribe the appropriate dose.

Please read section 3 of the Patient Leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

These medicines can only be obtained with a prescription.

**What benefits of Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution have been shown in studies?**

As dexamethasone sodium phosphate is a well-established substance, and its use in the treatment of the below indications is well-established, the applicant presented data from the scientific literature. The literature provided, confirmed the efficacy and safety of dexamethasone sodium phosphate in the treatment of:

- Where the natural corticosteroid levels have been reduced and they need to be replaced
- Reducing swelling on the brain which is not caused by a head injury
- If tests are being conducted for diseases which may decrease the 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
What are the possible side effects from Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution?

Like all medicines Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution may cause side effects in some people. The doctor should be informed straight away if:

- serious mental health problems are experienced such as
  - feeling depressed or suicidal
  - feeling high (mania) or moods that go up and down
  - feeling anxious, having problems sleeping, difficulty in thinking or being confused and losing memory
  - feeling, seeing or hearing things that do not exist
- an allergic reaction to Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution is experienced which has the following side effects
  - red and lumpy skin rash
  - difficulty breathing
  - swelling of the face, mouth, lips or eyelids.

A full list of all the side effects reported with Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution can be found in section 4 of the package leaflets.

Why are Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution approved?

The use of dexamethasone has an acceptable level of safety and is well-established in the treatment of a wide variety of disorders requiring glucocorticoid therapy. Therefore the benefit of using Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution in certain conditions outweighs the identified risks.

What measures are being taken to ensure the safe and effective use of Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution?
A risk management plan has been developed to ensure that Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflets for Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution

Cyprus, Greece and the United Kingdom agreed to grant a Marketing Authorisation for Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution on 20 April 2014. A Marketing Authorisation was granted in the UK on 19 May 2014.

The full PAR for Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution follows this summary. For more information about treatment with Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in July 2014.
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Module 1
Information about initial procedure

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Dexamethasone 20mg/5ml Oral Solution |
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<td>Focus Pharmaceuticals Ltd</td>
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<td>First Avenue</td>
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Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been 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 for products that are 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 these applications for Dexamethasone 10mg/5ml Oral Solution (PL 20046/0277; UK/H/5437/001/DC) and Dexamethasone 20mg/5ml Oral Solution (PL 20046/0276; UK/H/5437/002/DC) could be approved. These applications for Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution were submitted according to Article 10(a) of Directive 2001/83/EC, as amended, on the basis of “well-established use” via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Greece and Cyprus as Concerned Member States (CMS).

Dexamethasone 10mg/5ml Oral Solution and Dexamethasone 20mg/5ml Oral Solution are prescription-only medicines (legal classification POM). Both medicines are for oral use only.

Dexamethasone 10mg/5ml and 20mg/5ml Oral Solutions contain the active ingredient dexamethasone (as dexamethasone sodium phosphate) which is synthetic adrenocorticosteroid with highly potent and long-acting glucocorticoid activity. It has anti-inflammatory and immunosuppressive activity and is indicated in a wide range of conditions where symptomatic anti-inflammatory/immunosuppressive therapy is required. The anti-inflammatory potency of dexamethasone on a weight for weight basis is 7 times greater than that of prednisolone.

Dexamethasone 10mg/5ml and 20mg/5ml Oral Solutions are 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, 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.

No new non-clinical or clinical studies were conducted, which is acceptable given that these applications are for products containing an active of well-established use and are based on bibliographic data.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved at the end of procedure (Day 210) on 20 April 2014. After a subsequent national phase, licences were granted in the UK on 19 May 2014.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Dexamethasone 10mg/5ml Oral Solution  
Dexamethasone 20mg/5ml Oral Solution |
<table>
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<tr>
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<td>Dexamethasone sodium phosphate</td>
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<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Glucocorticoids (H02A B02)</td>
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<td>PL 20046/0276</td>
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<td>PL 20046/0277</td>
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| Name and address of the authorisation holder     | Focus Pharmaceuticals Ltd  
Unit 5, Faraday Court  
First Avenue  
Centrum 100  
Burton upon Trent  
Staffordshire  
DE14 2WX |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance - dexamethasone sodium phosphate

INN: Dexamethasone sodium phosphate

Chemical names:
- 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione disodium phosphate
- (11β,16α)-9-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione 21-(dihydrogen phosphate) disodium salt
- 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione disodium 21-phosphate

Structure:

![Chemical Structure Image]

Molecular formula: C_{22}H_{28}FNa_{2}O_{8}P

Molecular weight: 516.4 g/mol

Appearance: White to practically white powder

Solubility:
- Freely soluble in water, slightly soluble in alcohol, very slightly soluble in dioxane, practically insoluble in dichloromethane and in ether, insoluble in chloroform.

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 Medicine and Healthcare (EDQM) Certificate of Suitability.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients, as follows:
- Propylene glycol (E1520), liquid maltitol (E965), mint flavour, liquid sorbitol (non-crystallising) (E420), sodium citrate dihydrate (E331), EDTA disodium, sucralose, sodium hydroxide solution 1N (as pH adjuster) and purified water.

All excipients used comply with their respective European Pharmacopoeia monograph, with the exception of the mint flavouring, which is compliant with a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients are sourced from 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 sodium phosphate 10mg/5ml and 20mg/5ml Oral Solution that is similar in physico-chemical characteristics to other currently approved dexamethasone oral solution products.

A satisfactory account of the pharmaceutical development has been provided.

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished products.

Process validation has been carried out on three commercial-scale batches of each product. The results are satisfactory.

**Finished Product Specification**

The finished product specifications 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.

**Container-Closure System**

The finished product is packaged in the following containers:

- Dexamethasone 10mg/5ml Oral Solution is available in amber (Type III) glass bottles, with child-resistant, tamper-evident high-density polyethylene screw caps, which have a low-density polyethylene seals and a 5ml graduated Oral dosing syringe and a “press in” syringe/bottle adaptor.
- Dexamethasone 20mg/5ml oral Solution is available in amber (Type III) glass bottles, with child-resistant, tamper-evident high-density polyethylene screw caps, which have a low-density polyethylene seals and a 3ml graduated oral dosing syringe and a “press in” syringe/bottle adaptor.
- Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution are available in pack sizes of 30ml or 50ml bottles.

The Marketing Authorisation Holder has stated that not all pack sizes are intended for marketing. However, they have committed to providing the relevant licensing authority with the mock-ups for any pack size before marketing it in that country.

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 foodstuff.

**Stability of the product**

Stability studies were performed, in accordance with current guidelines on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 24 months for the unopened product which reduces to 3 months after first opening with storage conditions “Do not store above 25°C. Do not refrigerate and store in the original package in order to protect from light”.

**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 SmPCs, PILs and labels are acceptable from a pharmaceutical perspective.
Package leaflets have been submitted to the MHRA. A bridging report has been submitted which supports the PILs for these applications on the basis that they are similar in layout and design to the PIL for Dexamethasone 2mg/5ml oral solution; PL20046/0260; UK/H/5139/001/DC. The Marketing Authorisation Holder follows a house style which covers a common design and layout for all their PILs. This house style has been tested 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 in house style for the package leaflets are 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 it contains.

**Marketing Authorisation Application (MAA) form**
The MAA forms are satisfactory from a pharmaceutical perspective.

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

**Conclusion**
The grant of Marketing Authorisations is recommended.

### 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.

Suitable justification has been provided for the non-submission of an environmental risk assessment. As these products are intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected.

There are no objections to the approval of these products from a non-clinical viewpoint.

### III.3 CLINICAL ASPECTS
As the clinical pharmacology, efficacy and safety of dexamethasone sodium phosphate are well-known, no new clinical studies are required and none have been provided.

The bioequivalence and the biowaiver requirements were considered in the context of assessing the similarity of the product to other Dexamethasone products on the market. However, the application was submitted as a well-established use application.

**Efficacy**
No new clinical data on efficacy have been submitted and none are required for applications of this type. The well-established efficacy of dexamethasone has been adequately described using literature data.

**Safety**
No new safety data were submitted and none were required. Adequate literature data have been supplied to support the well-established safety profile of dexamethasone.

**SmPC, PIL and Labels**
The SmPCs, PILs and labels are acceptable from a clinical perspective.
**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 risk management plan has been developed to ensure that Dexamethasone 10mg/5ml and 20mg/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 leaflets for Dexamethasone 10mg/5ml and 20mg/5ml Oral Solution, including the appropriate precautions to be followed by healthcare professionals and patients.

**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.

**Conclusion**
The grant of Marketing Authorisations is recommended.

**IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**

**QUALITY**
The important quality characteristics of Dexamethasone 10mg/5ml and 20mg/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 and none are required for applications of this type.

**CLINICAL**
No new clinical data were submitted and none were required for these applications. The efficacy of the active, dexamethasone sodium phosphate is well described and no new clinical studies were required. The applicant has summarised the current state of knowledge in their literature review. The literature review identified no new or unexpected safety issues or concerns.

The SmPCs, PILs and labelling are satisfactory and consistent with those of other similar marketed products.

**BENEFIT-RISK ASSESSMENT**
The qualities of the products are acceptable, and no new non-clinical or new 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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