Public Assessment Report

UKPAR

DEXAMETHASONE 2 MG SOLUBLE TABLETS
DEXAMETHASONE 4 MG SOLUBLE TABLETS
DEXAMETHASONE 8 MG SOLUBLE TABLETS

(dexamethasone sodium phosphate)

PL 25258/0161-0163

Glenmark Pharmaceuticals Europe Limited
LAY SUMMARY
Dexamethasone 2 mg soluble tablets
Dexamethasone 4 mg soluble tablets
Dexamethasone 8 mg soluble tablets
(dexamethasone sodium phosphate)

This is a summary of the public assessment report (PAR) for Dexamethasone 2 mg soluble tablets (PL 25258/0161), Dexamethasone 4 mg soluble tablets (PL 25258/0162) and Dexamethasone 8 mg soluble tablets (PL 25258/0163). It explains how the applications for Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets were assessed and their authorisation recommended as well as their conditions of use. It is not intended to provide practical advice on how to use Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets.

For practical information about using Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets and what are they used for?
Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets are medicines with ‘well-established use’. This means that the medicinal use of the active substance of Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets has been well-established in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets are used for one of the following:

- where natural corticosteroid levels have been reduced and patients need to replace them
- where swelling of the brain has occurred
- if patients are having tests for diseases which may decrease their 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
  - after organ transplants and to prevent nausea and vomiting following chemotherapy
How do Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets work?
These medicines contain the active substance dexamethasone (as dexamethasone sodium phosphate). Dexamethasone 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 the body with extra corticosteroid (such as dexamethasone) is an effective way to treat various illnesses involving inflammation in the body. Dexamethasone soluble tablets reduce this inflammation, which could otherwise go on making the condition worse.

How are Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets used?
These medicines can only be obtained with a prescription.

In adults, the usual dose of dexamethasone is 0.5 mg to 10 mg each day. If a doctor wishes a patient to take less than 2 mg per day, they will prescribe the patient a different dexamethasone product.

In children the usual dose is a single dose on alternate days.

When Dexamethasone soluble tablets are being given as part of some hospital tests, the dose given will be 2 mg, for a short period of time.

Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets are only to be taken by mouth. A doctor will prescribe the most appropriate dose to treat each condition. The tablets should be taken as a drink after dissolving them in a glass of water and should be taken as a single dose each morning, unless the doctor has told the patient otherwise.

These medicines should always be taken exactly as the doctor instructs. These instructions will have been added to the dispensing label by the patient’s pharmacist. Patients should check with their doctor or pharmacist if they are not sure how to take this medicine.

What benefits of Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets have been shown in studies?
As dexamethasone sodium phosphate is a well-known substance and its use in the licensed indications is well established, the applicant has presented data from the scientific literature. The literature provided confirmed the efficacy and safety of dexamethasone sodium phosphate for use in the licensed indications.

What are the possible side effects of Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets?
Like all medicines, these medicines can cause side effects, although not everybody gets them.

For the full list of side effects reported with Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets, see section 4 of the package leaflet, available on the MHRA website

For the full list of restrictions, see the package leaflet.

Why are Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets approved?
The MHRA concluded that, in accordance with EU requirements, the benefits of Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets outweigh the identified risks and recommended that the products be approved for use.

What measures are being taken to ensure the safe and effective use of Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets?
A risk management plan has been developed to ensure that Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets are 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 2 mg, 4 mg and 8 mg soluble tablets, including the appropriate precautions to be followed by healthcare professionals and
Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

**Other information about Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets**

Marketing Authorisations were granted in the UK on 14 September 2015.

The full PAR for Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets follows this summary. For more information about treatment with Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in October 2015.
**SCIENTIFIC DISCUSSION**

**TABLE OF CONTENTS**

<table>
<thead>
<tr>
<th>I</th>
<th>Introduction</th>
<th>Page 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Quality aspects</td>
<td>Page 8</td>
</tr>
<tr>
<td>III</td>
<td>Non-clinical aspects</td>
<td>Page 13</td>
</tr>
<tr>
<td>IV</td>
<td>Clinical aspects</td>
<td>Page 13</td>
</tr>
<tr>
<td>V</td>
<td>User consultation</td>
<td>Page 15</td>
</tr>
<tr>
<td>VI</td>
<td>Overall conclusion, benefit/risk assessment and</td>
<td>Page 15</td>
</tr>
<tr>
<td></td>
<td>recommendation</td>
<td></td>
</tr>
</tbody>
</table>
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products regulatory Agency (MHRA) granted Glemark Pharmaceuticals Europe Limited Marketing Authorisations for the medicinal products Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets (PL 25258/0161-0163) on 14 September 2015.

These products are prescription-only medicines (legal classification POM).

The applications were submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be applications for products containing an active substance of well-established use.

During assessment of these national abridged applications major objections were raised with respect to the quality, efficacy and safety of the products. The applications were considered by the Committee on Human Medicines (CHM) at the meeting in October 2014. In response to the CHM advice the applicant has provided a bioequivalence study to support bridging of clinical efficacy and safety from the extensive literature on dexamethasone base to the ester form of the drug, dexamethasone sodium phosphate. The information provided was adequate and the issues were resolved. The procedure was positively concluded on 14 September 2015.

Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets are indicated for use in certain endocrine and non-endocrine disorders, in certain cases of cerebral oedema and for diagnostic testing of adrenocortical hyperfunction, as follows:

**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.

These products contain the active substance dexamethasone (as dexamethasone sodium phosphate). Dexamethasone is a highly potent and long-acting glucocorticoid with negligible sodium retaining properties and is, therefore, particularly suitable for 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.

With the exception of the bioequivalence study, no new clinical or non-clinical studies were conducted, which is acceptable given that these are bibliographic applications for products containing an active ingredient of well-established use.

The MHRA 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.

A summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) have been provided with this application and these are satisfactory.
II QUALITY ASPECTS

II.1 Introduction
Each Dexamethasone 2 mg soluble tablet contains 2 mg dexamethasone as dexamethasone sodium phosphate. The tablets are salmon coloured and oblong shaped.

Each Dexamethasone 4 mg soluble tablet contains 4 mg dexamethasone as dexamethasone sodium phosphate. The tablets are salmon coloured, round and biconvex.

Each Dexamethasone 8 mg soluble tablet contains 8 mg dexamethasone as dexamethasone sodium phosphate. The tablets are salmon coloured, round, biconvex and engraved with ‘8’.

The finished products are packaged in aluminium foil blisters and packed in cartons containing 10 or 30 tablets.

The other ingredients are sodium bicarbonate, disodium citrate 1.5 hydrate, povidone K30, sodium saccharin, sodium benzoate and sunset yellow (E110).

The disodium citrate 1.5 hydrate is controlled in line with the British Pharmacopoeia. The sunset yellow (E110) complies with in-house specifications. All other excipients comply with their respective European Pharmacopoeia monographs. None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

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

II.2 Drug substance
INN: Dexamethasone sodium phosphate
Chemical name(s): 9-Fluoro-11β,17-dihydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-yl disodium phosphate.

Structure:

![Dexamethasone Structure](image)

Molecular formula: $C_{22}H_{28}FNa_2O_8P$
Molecular weight: 516.4
Appearance: White or almost white very hygroscopic powder.
Solubility: Freely soluble in water, slightly soluble in ethanol (96%), practically insoluble in methylene chloride.

All aspects of the manufacture and control of this active substance is covered by a European Directorate for the quality of Medicines (EDQM) Certificate of Suitability (CEP).
II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate a new pharmaceutical form as a soluble tablet containing 2 mg, 4 mg and 8 mg of dexamethasone.

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 product.

Process validation has been carried out on two pilot-scale batches of each strength of finished product. The results are satisfactory. A process validation scheme has been provided for the first three commercial batches of each strength of finished product.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the product
Stability studies were performed, in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing.

The results from these studies support a shelf-life 2 years when stored in the original packaging, with no special storage requirements.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that Marketing Authorisations are granted for Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website.
Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets

Carton:

Dexamethasone 2 mg soluble tablets
Dexamethasone

30 tablets

Dexamethasone 2 mg soluble tablets
Dexamethasone

2 mg
Each tablet contains 2 mg dexamethasone as the sodium phosphate ester

Place dispensing label here

Glenmark

30 tablets

Dexamethasone 2 mg soluble tablets
Dexamethasone

2 mg
Each tablet contains 2 mg dexamethasone as the sodium phosphate ester

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
The medicinal product does not require any special temperature storage conditions. Store in the original package.

Glenmark Pharmaceuticals Europe Limited
Laxmi House, 2B Draycott Avenue, Kenton,
Middlesex, HA3 0BU, United Kingdom
PL 25258/0161

Blister:

Dexamethasone 2 mg soluble tablets
Dexamethasone

Glenmark Pharmaceuticals Europe Limited
Laxmi House, 2B Draycott Avenue, Kenton,
Middlesex, HA3 0BU, United Kingdom

Dexamethasone 2 mg soluble tablets
Dexamethasone

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Dexamethasone

Glenmark Pharmaceuticals Europe Limited
Laxmi House, 2B Draycott Avenue, Kenton,
Middlesex, HA3 0BU, United Kingdom
PAR Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets

Carton:

Dexamethasone 4 mg soluble tablets
Dexamethasone
30 tablets

Dexamethasone 4 mg soluble tablets
Dexamethasone
4 mg
Each tablet contains 4 mg dexamethasone as the sodium phosphate ester
30 tablets

Dexamethasone 4 mg soluble tablets
Dexamethasone
4 mg
Each tablet contains 4 mg dexamethasone as the sodium phosphate ester
30 tablets

Blister:

Dexamethasone 4 mg soluble tablets
Dexamethasone
Glenmark Pharmaceuticals Europe Limited
Laxmi House, 2B Draycott Avenue, Kenton, Middlesex, HA3 0BU, United Kingdom

Dexamethasone 4 mg soluble tablets
Dexamethasone
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Dexamethasone 4 mg soluble tablets
Dexamethasone
Glenmark Pharmaceuticals Europe Limited
Laxmi House, 2B Draycott Avenue, Kenton, Middlesex, HA3 0BU, United Kingdom
Dexamethasone 2 mg, 4 mg, and 8 mg soluble tablets

Carton:

Dexamethasone 8 mg soluble tablets
Dexamethasone
30 tablets

Each tablet contains 8 mg dexamethasone as the sodium phosphate ester. It also contains sodium.

Read the package leaflet before use.

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

This medicinal product does not require any special temperature storage conditions. Store in the original package.

Glenmark Pharmaceuticals Europe Limited
Laxmi House, 2B Draycott Avenue, Kenton, Middlesex, HA3 0BU, United Kingdom
PL 25268/0163

Blister:

Dexamethasone 8 mg soluble tablets
Dexamethasone

Glenmark Pharmaceuticals Europe Limited
Laxmi House, 2B Draycott Avenue, Kenton, Middlesex, HA3 0BU, United Kingdom

Dexamethasone 8 mg soluble tablets
Dexamethasone

Glenmark Pharmaceuticals Europe Limited
Laxmi House, 2B Draycott Avenue, Kenton, Middlesex, HA3 0BU, United Kingdom
III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of dexamethasone are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

III.2 Pharmacology
No new pharmacology data are required for these applications and none have been submitted.

III.3 Pharmacokinetics
No new pharmacokinetic data are required for these applications and none have been submitted.

III.4 Toxicology
No new toxicology data are required for these applications and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)
As it is anticipated that these products will replace products that are already marketed, no increase in environmental exposure to dexamethasone is anticipated. Thus the absence of an ERA is accepted.

III.6 Discussion of the non-clinical aspects
It is recommended that Marketing Authorisations are granted for Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets.

IV. CLINICAL ASPECTS

IV.1 Introduction
With the exception of the bioequivalence study, no new clinical data have been submitted and none are required for applications of this type. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of dexamethasone. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
The applicant has submitted a clinical pharmacokinetic study to support bridging of clinical efficacy and safety from the extensive literature on dexamethasone base tablets to the ester form of the drug, dexamethasone sodium phosphate.

STUDY:
An open label, balanced, randomised, single oral dose, two-treatment, two-sequence, two-period, two-way crossover, study to compare the pharmacokinetics of the applicant’s test product Dexamethasone 8 mg soluble tablets (Glenmark Pharmaceuticals Europe Limited) versus the reference product Dexamethasone Tablets BP 2 mg (Organon Laboratories Limited) in healthy adult subjects under fasting conditions.

The subjects were administered a single dose of either the test or the reference product under fasting conditions. The test product was administered as a liquid while the reference product was given as 4 solid 2 mg tablets. Blood samples were collected for plasma levels before dosing and up to and including 24 hours after each administration. The washout period between the treatment phases was 4 days. A summary of the main pharmacokinetic results is presented below:
Compared with the reference product, the 90 % confidence intervals for the test product are within 80.00-125.00 % for AUC, however the results for $C_{\text{max}}$ fall outside the acceptance criteria. The high upper limit for the 90% confidence interval for $C_{\text{max}}$ could be attributed to the high solubility of the active substance dexamethasone sodium phosphate and the soluble tablet formulation of the drug product, resulting in faster absorption compared to the solid tablet formulation.

These were bibliographic applications submitted under Article 10a of Directive 2001/83/EC, as amended, for products containing an active substance of well-established use. For these applications, overall drug exposure, as reflected in equivalence in the pharmacokinetic parameter AUC, is sufficient to bridge clinical efficacy and safety from the extensive bibliographic information provided on dexamethasone base tablets to Dexamethasone 8 mg soluble tablets.

As these products meet the bio-waiver criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), the results and conclusions of the bioequivalence study on the 8 mg strength can be extrapolated to the 2 mg and 4 mg strength soluble tablets.

### IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none are required for an application of this type.

### IV.4 Clinical efficacy
No new data on efficacy have been submitted and none are required for an application of this type.

### IV.5 Clinical Safety
No new data on safety have been submitted and none are required for an application of this type.

### IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The applicant has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC, as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:
IV.7 Discussion of the clinical aspects
It is recommended that Marketing Authorisations are granted for Dexamethasone 2 mg, 4 mg and 8 mg soluble tablets.

V. USER CONSULTATION
The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results show that the package leaflet meets the criteria for readability, as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION AND 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 assessment is therefore considered to be positive.
Annex 1  Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Y/N (version)</td>
</tr>
</tbody>
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