Public Assessment Report

Decentralised Procedure

Dexamethasone 3.3 mg/ml, solution for injection
(dexamethasone sodium phosphate)

UK/H/6324/001/DC

UK licence no: PL 41947/0030

ELC GROUP s.r.o
LAY SUMMARY

Dexamethasone 3.3 mg/ml, solution for injection
(dexamethasone sodium phosphate)

This is a summary of the Public Assessment Report (PAR) for Dexamethasone 3.3 mg/ml, solution for injection (PL 41947/0030; UK/H/6324/001/DC). It explains how Dexamethasone 3.3 mg/ml, solution for injection 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 this product. The product will be referred to as Dexamethasone solution for injection throughout the remainder of this summary.

For practical information about using Dexamethasone solution for injection, patients should read the package leaflet or contact their doctor or pharmacist.

What is Dexamethasone solution for injection and what is it used for?
Dexamethasone solution for injection is a ‘generic medicine’. This means that Dexamethasone solution for injection is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Decadron 3.3mg/mL injection.

Corticosteroids are given to patients for a variety of conditions where their abilities to reduce inflammation and suppress the immune system are valuable. These conditions may include Crohn’s disease, asthma, shock, anaphylaxis, tuberculosis, arthritis, osteoarthritis, and skin disorders including acne.

How does Dexamethasone solution for injection work?
The active substance in Dexamethasone solution for injection is dexamethasone (as sodium phosphate). Dexamethasone belongs to a group of medicines called steroids (specifically known as corticosteroids). Corticosteroids occur naturally in the body and help to maintain health and well-being. Synthetic steroids such as dexamethasone work by mimicking some of their actions to treat disease.

How is Dexamethasone solution for injection used?
This medicine will be given as an injection either intravenously (injection into a vein), intramuscularly (injection into a muscle) or directly into a joint or soft tissue, by a healthcare professional.

The patient’s doctor will decide what the appropriate dose for the condition, and may alter their patient’s dose depending on how he or she responds. The usual initial dose ranges from 0.4mg-16.6 mg (0.125-5ml) per day, with repeat dosing depending on the patient’s condition.

For some patients, the medicine may be given as an injection into the painful area itself, usually once every 3 to 5 days or once every 2-3 weeks depending on the patient’s response.

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

What benefits of Dexamethasone solution for injection have been shown in studies?
No additional studies were needed as Dexamethasone solution for injection is a generic medicine that contains the same active substance in the same concentration as the reference medicine, Decadron 3.3mg/mL injection. For this reason, Dexamethasone solution for
injection is expected to be bioequivalent with the reference medicine. Two medicines are considered bioequivalent when they produce the same levels of active substance in the body.

**What are the possible side effects of Dexamethasone solution for injection?**
Because Dexamethasone solution for injection is a generic medicine, its possible side effects are taken as being the same as those of the reference medicine, Decadron 3.3mg/mL injection.

For the full list of all side effects reported with Dexamethasone solution for injection, see Section 4 of the package leaflet available on the MHRA website.

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

**Why is Dexamethasone solution for injection approved?**
It was concluded that, in accordance with EU requirements, Dexamethasone solution for injection has been shown to have comparable quality and is considered bioequivalent to Decadron 3.3mg/mL injection. Therefore, the MHRA decided that, for Dexamethasone solution for injection, the benefits are greater than the risks and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Dexamethasone solution for injection?**
A Risk Management Plan (RMP) has been developed to ensure that Dexamethasone solution for injection is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet for this product, 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 and healthcare professionals will be monitored and reviewed continuously, as well.

**Other information about Dexamethasone solution for injection**
On 15 June 2017, Malta, and the UK agreed to grant a Marketing Authorisation for Dexamethasone solution for injection. Following a subsequent national phase, a Marketing Authorisation was granted on 10 July 2017 in the UK.

The full PAR for Dexamethasone solution for injection follows this summary.

For more information about treatment with Dexamethasone solution for injection, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in August 2017.
<table>
<thead>
<tr>
<th>I</th>
<th>Introduction</th>
<th>Page 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Quality aspects</td>
<td>Page 7</td>
</tr>
<tr>
<td>III</td>
<td>Non-clinical aspects</td>
<td>Page 9</td>
</tr>
<tr>
<td>IV</td>
<td>Clinical aspects</td>
<td>Page 9</td>
</tr>
<tr>
<td>V</td>
<td>User consultation</td>
<td>Page 11</td>
</tr>
<tr>
<td>VI</td>
<td>Overall conclusion, benefit/risk assessment and recommendation</td>
<td>Page 11</td>
</tr>
</tbody>
</table>

Table of content of the PAR update for MRP and DCP

Page 17
I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member State (CMS) considered that the application for Dexamethasone 3.3 mg/ml, solution for injection (PL 41947/0030; UK/H/6324/001/DC) could be approved.

This is a decentralised abridged application submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of the reference product, Decadron 3.3mg/mL injection, which was granted a Marketing Authorisation under exceptional circumstances to Merck, Sharp and Dohme Limited on July 1987 following a national procedure (PL 00025/5045R).

Dexamethasone 3.3 mg/ml, solution for injection is a ‘prescription only medicine’ (legal status “POM”) containing the active substance dexamethasone sodium phosphate which is indicated for use in certain endocrine and non-endocrine disorders responsive to corticosteroid therapy.

- **Systemic administration**: Dexamethasone 3.3 mg/ml, solution for injection is recommended for systemic administration by intravenous or intramuscular injection when oral therapy is not feasible or desirable in the following conditions.

- **Endocrine disorders**
  - *Primary or secondary adrenocortical insufficiency* (hydrocortisone or cortisone is the first choice, but synthetic analogues may be used with mineralocorticoids where applicable and, in infancy, mineralocorticoid supplementation is particularly important).

- **Non-endocrine disorders**
  - Dexamethasone 3.3 mg/ml, solution for injection may be used in the treatment of non-endocrine corticosteroid-responsive conditions, including:
    - **Allergy and anaphylaxis**: Angioneurotic oedema and anaphylaxis.
    - **Gastro-intestinal**: Crohn's disease and ulcerative colitis.
    - **Infection (with appropriate chemotherapy)**: Miliary tuberculosis and endotoxic shock.
    - **Neurological disorders**: Raised intracranial pressure secondary to cerebral tumours and infantile spasms.
    - **Respiratory**: Bronchial asthma and aspiration pneumonitis.
    - **Skin disorders**: Toxic epidermal necrolysis.

- **Shock**: Adjunctive treatment where high pharmacological doses are needed. Treatment is an adjunct to, and not a substitute for, specific and supportive measures the patient may require. Dexamethasone 3.3 mg/ml, solution for injection has been shown to be beneficial when used in the early treatment of shock, but it may not influence overall survival.

- **Local administration**
  - Dexamethasone 3.3 mg/ml, solution for injection is suitable for intra-articular or soft-tissue injection as adjunctive therapy for short-term administration in:
• *Soft-tissue disorders* such as carpal tunnel syndrome and tenosynovitis.

• *Intra-articular disorders* such as rheumatoid arthritis and osteoarthritis with an inflammatory component.

• Dexamethasone 3.3 mg/ml, solution for injection may be injected intra-lesionally in selected skin disorders such as cystic acne vulgaris, localised lichen simplex, and keloids.

Dexamethasone sodium phosphate is a glucocorticosteroid which has anti-inflammatory and immunosuppressant activities. Dexamethasone possesses the actions and effects of other basic glucocorticoids and is among the most active members of its class.

Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastro-intestinal tract. They cause profound and varied metabolic effects and in addition, they modify the body's immune responses to diverse stimuli. Naturally-occurring glucocorticoids (hydrocortisone and cortisol), which also have salt-retaining properties, are used primarily for their potent anti-inflammatory effects in disorders of many organ systems.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

No new clinical data have been submitted and none are required for an application of this type. In line with the CPMP ‘guideline on the investigation of bioequivalence’ subpoint 5.1.6, parenteral solutions, document reference: CPMP/EWP/1401/98, a bioequivalence study was not necessary to support this application, as both test and reference products are solutions at the time of administration.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type 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.

The United Kingdom acted as RMS and Malta was the CMS.

All Member States agreed to grant a Market Authorisation for the above Dexamethasone 3.3 mg/ml, solution for injection on 15 June 2017. Following a subsequent national phase, the UK granted a Market Authorisation (PL 41947/0030) for this product on 10 July 2017.
II QUALITY ASPECTS

II.1 Introduction
Dexamethasone 3.3 mg/ml, solution for injection contains 3.3 mg dexamethasone (as sodium phosphate) per ml, which is equivalent to 4 mg dexamethasone phosphate or 4.37 mg dexamethasone sodium phosphate.

Each 2 ml contains 6.6 mg dexamethasone (as sodium phosphate) which is equivalent to 8 mg dexamethasone phosphate or 8.74 mg dexamethasone sodium phosphate.

Other ingredients consist of the pharmaceutical excipients creatinine, sodium citrate, citric acid hydrate, sodium hydroxide, water for injection.

The finished product is packaged in 1 ml clear glass ampoule placed in boxes of 5 or 10 ampoules. The finished product is also packaged into a 2 ml clear glass ampoule placed in boxes of 5 and 10 ampoules.

Not all pack sizes may be marketed, however, the marketing authorisation holder has agreed to provide mock-ups of any pack size to the relevant regulatory authorities before marketing.

All primary product packaging complies with the current requirements. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 DRUG SUBSTANCES
dexamethasone (as sodium phosphate)

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

Structure:

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

Molecular Weight: 516.4

Appearance: A white or 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.

All aspects of the manufacture and control of the active substance, dexamethasone (as sodium phosphate), are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.
II.3 DRUG PRODUCT

Pharmaceutical development

The objective of the development programme was to formulate a concentrate solution for infusion containing dexamethasone (as sodium phosphate) 3.3 mg per ml of solution, which is comparable in performance to the originator product, Decadron 3.3mg/mL injection (Merck, Sharp and Dohme Limited). A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs, except for creatinin which is controlled to the United States Pharmacopoeia.

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.

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

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 a commercial-scale batch size and has shown satisfactory results. The marketing authorisation holder (MAH), has committed to perform additional process validation studies on future commercial-scale batches.

Finished Product Specification

The finished product specification is acceptable. Test methods have been described that have been adequately validated. Batch data that comply with the release specification have been provided. European Pharmacopoeia reference standards are used, where available. Representative Certificates of Analysis have been provided.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for the unopened product (After opening: the product must be used immediately), with the storage conditions, “Store below 25°C. Store in the outer pack in order to protect from light”.

From a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution and dilution have taken place in controlled validated aseptic conditions. Chemical and physical in-use stability has been demonstrated for 48 hours at 25°C protected from light when diluted with the infusion fluids.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that a Marketing Authorisation is granted for Dexamethasone 3.3 mg/ml, solution for injection.
III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of the active substance dexamethasone are well-known. No new non-clinical data have been submitted for this application and none are required. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
No new pharmacology data were submitted and none are required for an application of this type.

III.3 Pharmacokinetics
No new pharmacokinetic data were submitted and none are required for an application of this type.

III.4 Toxicology
No new toxicology data were submitted and none are required for an application of this type.

III.5 Environmental Risk Assessment
Since this product will be used as a substitute for other products that are currently on the market, no increase in environmental exposure is anticipated. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary. The applicant has provided suitable information to verify that no increase in the exposure of the environment to the active ingredient is to be expected.

III.6 Discussion on non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Dexamethasone 3.3 mg/ml, solution for injection.

IV CLINICAL ASPECTS

IV.1 Introduction
No new clinical studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant.

IV.2 Pharmacokinetics
In accordance, with the CPMP guideline “Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev.1 Corr ** - subpoint 5.1.6, parenteral solutions, document reference: CPMP/EWP/1401/98”, no bioequivalence data have been submitted with this application and none are required.

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 clinical safety have been submitted and none are required for an application of this type.

IV.6 Risk Management Plan (RMP)
The marketing authorisation holder has submitted an 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 3.3 mg/ml, solution for injection.

A summary of safety concerns, as approved in the RMP, are listed below:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
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</thead>
</table>
| Important identified risks | • Hypersensitivity  
|                           | • Increased susceptibility to and severity of infection (fungal, viral, bacterial, and parasitic)  
|                           | • Exacerbation/worsening of chickenpox  
|                           | • Exacerbation/worsening of measles  
|                           | • Live virus vaccines and reduced serum antibody response from inactivated viral or bacterial vaccines  
|                           | • Ocular toxicity including subcapsular cataract, glaucoma  
|                           | • Electrolyte disturbance including hypokalaemia  
|                           | • Adrenal suppression  
|                           | • Withdrawal symptoms  
|                           | • Corticosteroid worsening of underlying conditions (e.g. diabetes mellitus, osteoporosis, myopathy)  
|                           | • Severe psychiatric adverse reactions  
|                           | • Growth retardation in children  
|                           | • Neurodevelopmental adverse events in pre-term neonates  
|                           | • Drug interactions  
| Important potential risks | • Tumour lysis syndrome  
| Missing information       | • Lactation  

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.
IV.7 Discussion of the clinical aspects
It is recommended that a Marketing Authorisation is granted for Dexamethasone 3.3 mg/ml, solution for injection.

V USER CONSULTATION
A user consultation with target patient groups on the package leaflet has been performed and the results submitted in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

VI. OVERALL CONCLUSION AND BENEFIT RISK ASSESSMENT AND RECOMMENDATION
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. As the product consists of an aqueous solution for intravenous (IV), intramuscular (IM), or intraarticular (IA) use containing the same active substance and same concentration as the currently approved product Decadron 3.3mg/mL injection, and the excipients are not known to interact with the drug substance nor to otherwise affect the disposition of the drug substance, bioequivalence studies are not needed.

The benefit-risk is, therefore, considered to be positive.

PRODUCT LITERATURE
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisatons at a national level are available on the MHRA website.

The approved labelling for Dexamethasone 3.3 mg/ml, solution for injection is shown below:
Dexamethasone 3.3 mg/ml, solution for injection

Solution for injection
Dexamethasone (as sodium phosphate)
Each 1 ml ampoule contains 3.3 mg of dexamethasone (as sodium phosphate) which is equivalent to 4 mg of dexamethasone phosphate or 4.37 mg dexamethasone sodium phosphate.
Excipients: Creatinine, sodium citrate, sodium hydroxide, citric acid hydrate, water for injections.
Store below 25°C. Store in the outer pack to protect from light.

MA Holder:
ELC GROUP t.r.o
Karolínska 650/1
186 00 Prague 8
Czech Republic

POM
Intravenous use
Intramuscular use
Intraarticular use

x 10

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Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report
(Type II variations, PSURs, commitments)

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