Public Assessment Report

UKPAR

DEXAMETHASONE 3.3 MG/ML SOLUTION FOR INJECTION
DEXAMETHASONE 6.6 MG/ML SOLUTION FOR INJECTION
DEXAMETHASONE 8.3 MG/ML SOLUTION FOR INJECTION
(dexamethasone sodium phosphate)

UK Licence No: PL 01502/0079-81

Hameln Pharmaceuticals Limited
LAY SUMMARY
Dexamethasone 3.3 mg/ml solution for injection
Dexamethasone 6.6 mg/ml solution for injection
Dexamethasone 8.3 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 01502/0079), Dexamethasone 6.6 mg/ml solution for injection (PL 01502/0080) and Dexamethasone 8.3 mg/ml solution for injection (PL 01502/0081). It explains how the applications for these medicines 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 these medicines.

For practical information about using Dexamethasone 3.3 mg/ml, 6.6 ml/ml and 8.3 mg/ml solution for injection, patients should read the package leaflet or contact their doctor or pharmacist.

What are Dexamethasone 3.3 mg/ml, 6.6 ml/ml and 8.3 mg/ml solution for injection and what are they used for?
Dexamethasone 3.3 mg/ml, 6.6 ml/ml and 8.3 mg/ml solution for injection are ‘generic medicines’. This means that Dexamethasone 3.3 mg/ml, 6.6 ml/ml and 8.3 mg/ml solution for injection are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Decadron injection 3.3 mg/ml (PL 00025/5045R).

These products are given by injection to patients unable to take a tablet form of the medicine. They are usually used for patients with severe allergic reactions causing swelling of the face and throat, low blood pressure and collapse; shock caused by infection or severe tuberculosis (also with anti-infective treatments e.g. antibiotics); and raised pressure in the skull caused by tumours or infantile spasms.

Sometimes, the injection is given into the painful area itself e.g. inflammation of the joints (rheumatoid arthritis and osteoarthritis).

Dexamethasone 3.3 mg/ml solution for injection can sometimes also be given by injection under the skin (subcutaneously; SC) when used in palliative care to relieve certain symptoms including pain, tiredness, weight loss and feeling and being sick, when a tablet form of the medicine is unable to be given.

How do Dexamethasone 3.3 mg/ml, 6.6 ml/ml and 8.3 mg/ml solution for injection work?
These medicines contain the active ingredient dexamethasone sodium phosphate, which belongs to a group of medicines called steroids. Their full name is corticosteroids. Corticosteroids 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 reduces inflammation, which could otherwise go on making the condition worse.

How are Dexamethasone 3.3 mg/ml, 6.6 ml/ml and 8.3 mg/ml solution for injection used?
These medicines are only available on prescription.

The injection will be given by a nurse or doctor. A doctor will decide the correct dosage for the patient and how and when the injection will be given.

It can be dangerous to have the treatment stopped abruptly. After prolonged therapy the body may have gotten used to the administration of this medicine and may have reduced the normal production of hormones like the one contained in this medicine. How the treatment is stopped will depend on the disease that is being treated and how much has been given.

It may be necessary to reduce the amount of Dexamethasone 3.3 mg/ml solution for injection gradually until the patient stops having it altogether. A doctor has to make sure that the disease is unlikely to
relapse. Dosage must be adjusted if the patient is subjected to unusual stress (e.g. another illness, trauma or surgical procedures).

When the treatment is stopped too quickly, withdrawal symptoms like fever, muscle pain, joint pain and tiredness may occur. Too rapid a reduction following prolonged treatment can lead to insufficiency of hormone production in the adrenal gland and low blood pressure (symptoms of which can be tiredness, dizziness, headache, palpitation). In extreme cases this may be fatal.

In a few cases, mental health problems have occurred when doses are being lowered or stopped. If the patient suffers from any withdrawal symptoms, they should tell their doctor as soon as possible.

What benefits of Dexamethasone 3.3 mg/ml, 6.6 ml/ml and 8.3 mg/ml solution for injection have been shown in studies?
The company provided data from the published literature on the active substance. No additional studies were needed as Dexamethasone 3.3 mg/ml, 6.6 ml/ml and 8.3 mg/ml solution for injection are generic medicines that are given by injection and contain the same active substance as the reference medicine, Decadron injection 3.3 mg/ml (PL 00025/5045R).

What are the possible side effects of Dexamethasone 3.3 mg/ml, 6.6 ml/ml and 8.3 mg/ml solution for injection?
Like all medicines this medicine can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Dexamethasone 3.3 mg/ml, 6.6 ml/ml and 8.3 mg/ml solution for injection, see section 4 of the package leaflet. For the full list of restrictions, see the package leaflet.

Why were Dexamethasone 3.3 mg/ml, 6.6 ml/ml and 8.3 mg/ml solution for injection approved?
It was concluded that, in accordance with EU requirements, Dexamethasone 3.3 mg/ml, 6.6 mg/ml and 8.3 mg/ml Solution for Injection have been shown to have comparable quality and to be comparable to Decadron injection 3.3 mg/ml (PL 00025/5045R). Therefore, the view was that, as for Decadron injection 3.3 mg/ml (PL 00025/5045R), the benefit outweighs the identified risks.

What measures are being taken to ensure the safe and effective use Dexamethasone 3.3 mg/ml, 6.6 ml/ml and 8.3 mg/ml solution for injection?
Safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for these products 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 and reviewed continuously.

Other information about Dexamethasone 3.3 mg/ml, 6.6 ml/ml and 8.3 mg/ml solution for injection
Marketing Authorisations were granted in the UK to Hameln RDS GmbH on 13 June 2006 (PL 22856/0010-12). These applications underwent a Change of Ownership procedure on 04 December 2006 to Hameln Pharma Plus GmbH (PL 25215/0008-10).

These applications underwent a further Change of Ownership procedure on 01 March 2011 to the current Marketing Authorisation Holder, Hameln Pharmaceuticals Limited (PL 01502/0079-81).

The full PAR for Dexamethasone 3.3 mg/ml, 6.6 ml/ml and 8.3 mg/ml solution for injection follows this summary. For more information about treatment with Dexamethasone 3.3 mg/ml solution for injection, read the package leaflet, or contact your doctor or pharmacist.
This summary was last updated in October 2016.
# SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA considered that the applications for Dexamethasone 3.3 mg/ml, 6.6 mg/ml and 8.3 mg/ml solution for injection, for use in certain endocrine and non-endocrine disorders responsive to corticosteroid therapy, could be approved.

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

These applications were granted according to Article 10.1 of Directive 2001/83/EC, as amended, claiming essential similarity to Decadron Injection 3.3 mg/ml (PL 00025/5045R), which was originally granted a licence to Merck, Sharp and Dohme Limited on 31 July 1987.

These products contain the active substance dexamethasone sodium phosphate. 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 gastrointestinal 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 cortisone), which also have salt-retaining properties, are used primarily for their potent anti-inflammatory effects in disorders of many organ systems.

Dexamethasone has predominant glucocorticoid activity with little propensity to promote renal retention of sodium and water. Therefore it does not offer complete replacement therapy and must be supplemented with salt or desoxycorticosterone.

No new clinical or non-clinical studies were conducted, which is acceptable given that the applications were based on being essentially similar to an originator product that has been licensed for over 10 years.

The MHRA 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 this product.

Marketing Authorisations were granted in the UK to Hameln RDS GmbH on 13 June 2006 (PL 22856/0010-12). These applications underwent a Change of Ownership procedure on 04 December 2006 to Hameln Pharma Plus GmbH (PL 25215/0008-10).

These applications underwent a further Change of Ownership procedure on 01 March 2011 to the current Marketing Authorisation Holder, Hameln Pharmaceuticals Limited (PL 01502/0079-81).

QUALITY ASPECTS

II.1 Introduction

Dexamethasone 3.3 mg/ml solution for injection is a clear colourless solution. Each ml of solution for injection contains 4.00 mg of dexamethasone phosphate (as 4.37 mg dexamethasone sodium phosphate) equivalent to 3.32 mg of dexamethasone base.

The finished product is packaged in Type I clear glass ampoules containing either 1 ml or 2 ml of solution for injection, in pack sizes of 1, 5 or 10 ampoules. Not all pack sizes may be marketed.

Dexamethasone 6.6 mg/ml solution for injection is a clear colourless solution. Each ml of solution for injection contains 8.00 mg of dexamethasone phosphate (as 8.74 mg dexamethasone sodium phosphate) equivalent to 6.65 mg of dexamethasone base.
The finished product is packaged in Type I clear glass ampoules containing 5 ml of solution for injection, in pack sizes of 1, 5 or 10 ampoules. Not all pack sizes may be marketed.

Dexamethasone sodium phosphate 8.3 mg/ml solution for injection is a clear colourless solution. Each ml of solution for injection contains 10.00 mg of dexamethasone phosphate (as 10.93 mg dexamethasone sodium phosphate) equivalent to 8.31 mg of dexamethasone base.

The finished product is packaged in Type I clear glass ampoules containing 10 ml of solution for injection, in pack sizes of 1 or 5 ampoules. Not all pack sizes may be marketed.

Other ingredients consist of the pharmaceutical excipients, namely propylene glycol, disodium edetate, sodium hydroxide solution and water for injections.

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
rINN: Dexamethasone sodium phosphate
Chemical name(s): 9-Fluro-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 almost white, hygroscopic powder

All aspects of the manufacture and control of the active substance dexamethasone sodium phosphate from its starting materials are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious and stable products, with essential similarity to the reference product, Decadron Injection 3.3 mg/ml (PL 00025/5045R).

A satisfactory account of the pharmaceutical development has been provided.

All the 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 this product.
Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, 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 three pilot-scale batches of finished product. The results are satisfactory. The Marketing authorisation Holder has committed to providing satisfactory validation data for the first three consecutive production scale batches for each concentration manufactured after the approval of the Marketing Authorisations.

Finished Product Specification
The 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 specification.

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 2 years, with the special storage conditions of “Keep container in the outer carton. Do not freeze. Store below 25°C”.

From a microbiological point of view, the product should be used immediately after opening. 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 h at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Any unused portion of the product should be discarded immediately after use.
Chemical and physical in-use stability of dilutions has been demonstrated for 24 h at 25°C. Dilutions should be used within 24 hours and discarded after use.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that Marketing Authorisations are granted for Dexamethasone 3.3 mg/ml, 6.6 ml/ml and 8.3 mg/ml solution for injection.

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.

The approved labels are shown below:
Dexamethasone 3.3 mg/ml, 6.6 mg/ml and 8.3 mg/ml solution for injection

3.3 mg in 1 ml

Dexamethasone
3.3 mg/ml
Injection

3.3 mg in 1 ml

IV, IM, SC, intraarticular, intrabursal or intralesional use

PL 01502/0079

hameln pharmaceuticals ltd

46/70/62/76
Batch no:
Exp. date:

6.6 mg in 2 ml

Dexamethasone
3.3 mg/ml Injection

6.6 mg in 2 ml

5 ampoules

IV, IM, SC, intraarticular, intrabursal or intralesional use

PL 01502/0079

hameln pharmaceuticals ltd

9/11/59/2419

Batch no:
Exp. date:
III  NON-CLINICAL ASPECTS
III.1  Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of dexamethasone sodium phosphate are well known. As dexamethasone sodium phosphate is a widely used and well-known active substance, the applicant has not provided additional studies in support of their application. An overview based on literature review is, thus, appropriate.

No new non-clinical data have been supplied with these applications and none are required for applications of this type. The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.
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 these products are intended for generic substitution of products that are already marketed, no increase in environmental exposure to the active substance 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 3.3 mg/ml, 6.6 ml/ml and 8.3 mg/ml solution for injection.

IV. CLINICAL ASPECTS
IV.1 Introduction
No new efficacy or safety 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, citing the well-established clinical pharmacology, efficacy and safety of the active substance. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
No new pharmacokinetic data were submitted with this application and none were required. The products are to be administered as an aqueous solution containing the same active substance as the reference product.

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 Pharmacovigilance System
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.
IV.7 Discussion of the clinical aspects
It is recommended that a Marketing Authorisation is granted for Dexamethasone 3.3 mg/ml, 6.6 ml/ml and 8.3 mg/ml solution for injection.

V. USER CONSULTATION
The package leaflet has been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of 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 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 sodium phosphate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.
Steps taken after the initial procedure with an influence on the Public Assessment Report

<table>
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<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
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<th>Approval/non approval</th>
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<td>To add the subcutaneous route of administration and indication of palliative care from PL 01502/0101-0001 (a licence arising from an extension application to PL 01502/0079). Sections 4.1, 4.2, 4.4 &amp; 4.6 of the SmPC, as well as the label and PIL and have been updated.</td>
<td>PL 01502/0079-0030</td>
<td>SmPC/PIL</td>
<td>19/09/2016</td>
<td>20/09/2016</td>
<td>Approval</td>
<td>Y Annex I</td>
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</table>
Reference: PL 01502/0079 - 0030
Product: Dexamethasone 3.3 mg/ml solution for injection
Marketing Authorisation Holder: Hameln Pharmaceuticals Limited
Active Ingredient(s): Dexamethasone sodium phosphate

Reason:
Type IB variation to add the subcutaneous route of administration and palliative care indication from PL 01502/0101-0001 (a licence arising from an extension application to PL 01502/0079). Sections 4.1, 4.2, 4.4 & 4.6 of the SmPC, as well as the label and PIL have been updated.

The extension application was submitted to add the subcutaneous route of administration to allow administration by subcutaneous injection or Continuous Subcutaneous Infusion (CSCI).

For the subcutaneous route, the product is indicated as an alternative to the oral route when the latter is unacceptable or no longer feasible as follows:
• In palliative care, patients receiving corticosteroids for symptoms such as fatigue, anorexia, refractory nausea and vomiting or adjuvant analgesia and symptomatic treatment of cord compression or raised intracranial pressure.

Supporting Evidence
Revised SmPC fragments and an updated PIL and labelling have been provided.

Please refer to the PAR for PL 01502/0101 for the evidence submitted in support of the additional route of administration and indication.

Evaluation
The amended sections of the SmPC and PIL and the amended labelling are satisfactory.

Please refer to the PAR for PL 01502/0101 for the assessment of the evidence submitted in support of the additional route of administration and indication.

The current SmPC and PIL are available on the MHRA website.

Decision
Approved on 20 September 2016.