Dexamethasone 500 microgram Tablets

PL 42701/0001

UK PAR

TABLE OF CONTENTS

Lay Summary Page 2
Scientific discussion Page 4
Steps taken for assessment Page 14
Steps taken after the initial procedure - summary Page 15
LAY SUMMARY

Dexamethasone 500 microgram Tablets

This is a summary of the Public Assessment Report (PAR) for Dexamethasone 500 microgram Tablets (PL 42701/0001). It explains how the application for Dexamethasone 500 microgram Tablets was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Dexamethasone 500 microgram Tablets.

For practical information about using Dexamethasone 500 microgram Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Dexamethasone 500 micrograms Tablets and what are they used for?

Dexamethasone 500 microgram Tablets are a generic medicine. This means that Dexamethasone 500 microgram Tablets are similar to a reference medicine already authorised in the UK called Dexamethasone 500 microgram Tablets, previously known as Decadron 500 mcg Tablets (PL 17736/0119; Chemidex Pharma Limited trading as Essential Generics, UK), which was authorised in the UK following a change of ownership procedure of Decadron 500 mcg Tablets (PL 00025/5046R; Merck Sharp and Dohme Limited, UK) on 02 March 2009. Decadron 500 mcg Tablets (PL 00025/5046R; Merck Sharp and Dohme Limited, UK) was granted a Product Licence in the UK on 11 February 1987. This product was the subject of a Product Licence of Right (PLR); because Decadron 500 mcg Tablets were on the market before the Medicines Act 1968 came into force in 1971.

Dexamethasone 500 microgram Tablets contain the active substance, dexamethasone, which belongs to a group of medicines called steroids.

Some of the illnesses and conditions that dexamethasone is used for include:

- swelling of the brain and increased pressure in the brain caused by a tumour;
- severe allergic reactions;
- blood disorders such as leukaemia and haemolytic anaemia (a reduction in red blood cells which can make the skin pale yellow and cause weakness or breathlessness);
- sarcoidosis, an immune disease that can lead to excess levels of calcium and vitamin D in the body;
- inflammation of the heart in association with heart attack or heart surgery;
- intestinal disorders, e.g. Crohn’s disease, ulcerative colitis;
- respiratory disorders such as asthma;
- tuberculosis (together with appropriate chemotherapy);
- certain inflammatory skin and muscular disorders;
- inflammation of the eye;
- rheumatoid arthritis;
- kidney inflammation caused by SLE, a disease of the immune system.

How do Dexamethasone 500 microgram Tablets work?

Corticosteroids are hormones that are found naturally in the body that help to keep the body healthy and well. Boosting the body with extra corticosteroid, such as dexamethasone, is an effective way to treat various illnesses involving inflammation in the body. Dexamethasone lowers inflammation, which could otherwise go on making some conditions worse.

How is Dexamethasone 500 microgram Tablets used?

Dexamethasone 500 microgram Tablets are taken by mouth and must be swallowed with plenty of water, with or immediately after a meal to prevent upset stomach.

The tablets should be taken regularly as advised by the prescribing doctor to obtain maximum effect.
Please read section 3 of the package leaflet (PL) for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

Dexamethasone 500 microgram Tablets can only be obtained with a prescription.

**What benefits of Dexamethasone 500 microgram Tablets have been shown in studies?**
As Dexamethasone 500 microgram Tablets are a generic medicine, studies have been limited to tests to determine that Dexamethasone 500 microgram Tablets are bioequivalent to the reference medicine Decadron 500 mcg Tablets (Chemidex Pharma Limited, trading as Essentials Generics, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body. In addition, the Marketing Authorisation Holder (Trotwood Pharma Limited) provided data from the published literature on dexamethasone.

**What are the possible side effects from Dexamethasone 500 microgram Tablets?**
Like all medicines, Dexamethasone 500 microgram Tablets can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Dexamethasone 500 microgram Tablets, see section 4 of the package leaflet available on the MHRA website.

Also, for the full list of restrictions, see the package leaflet.

**Why are Dexamethasone 500 microgram Tablets approved?**
The MHRA concluded that, in accordance with EU requirements, the benefits of Dexamethasone 500 microgram Tablets outweigh the identified risks and recommended that the product be approved for use.

**What measures are being taken to ensure the safe and effective use of Dexamethasone 500 microgram Tablets?**
A risk management plan has been developed to ensure that Dexamethasone 500 microgram 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 500 microgram Tablets, 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 500 microgram Tablets.**
A Marketing Authorisation was granted in the UK on 26 November 2014.

The full PAR for Dexamethasone 500 microgram Tablets follows this summary.

For more information about treatment with Dexamethasone 500 microgram Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in January 2015.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

I Introduction Page 5
II Quality aspects Page 6
III Non-clinical aspects Page 9
IV Clinical aspects Page 10
V User consultation Page 13
VI Overall conclusion, benefit/risk assessment and recommendation Page 13
Scientific discussion

I INTRODUCTION

On 26 November 2014, the MHRA granted a Marketing Authorisation for the medicinal product Dexamethasone 500 microgram Tablets (PL 42701/0001) to Trotwood Pharma Limited. The product is a prescription-only medicine (POM).

Dexamethasone 500 microgram Tablets contain the active ingredient, dexamethasone which is a synthetic glucocorticosteroid (methylated derivative of fluoroprednisolone) which exhibits marked anti-inflammatory, anti-allergic, anti-inflammatory and immunosuppressive effects which are exploited in clinical use.

Dexamethasone is indicated as a treatment for certain endocrine and non-endocrine disorders, in certain cases of cerebral oedema, and for diagnostic testing of adrenocortical hyperfunction as detailed below:

Endocrine disorders: Primary or secondary adrenocortical insufficiency, congenital adrenal hyperplasia.

Non-endocrine disorders: Dexamethasone may be used in the treatment of non-endocrine corticosteroid responsive conditions including:

- Allergy and anaphylaxis: angioneurotic oedema, anaphylaxis;
- Arteritis collagenosis: polymyalgia rheumatica, polyarteritis nodosa;
- Blood disorders: haemolytic anaemia, leukaemia, myeloma;
- Cardiovascular disorders: post-myocardial infarction syndrome;
- Gastro-intestinal: Crohn’s disease and ulcerative colitis;
- Hypercalcaemia: sarcoidosis;
- Infections (with appropriate chemotherapy): miliary tuberculosis;
- Muscular disorders: polymyositis;
- Neurological disorders: raised intra-cranial, pressure secondary to cerebral tumours;
- Ocular disorders: anterior and posterior uveitis, optic neuritis;
- Renal disorders: Lupus nephritis;
- Respiratory disease: bronchial asthma, aspiration pneumonitis;
- Skin disorders: pemphigus vulgaris.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, initially using as a European Reference Product (ERP) Fortecortin 500 mcg Tablets, marketed by Merck Serono GmbH and authorized in Germany since December 1995. The BfArM confirmed that Fortecortin is legally acceptable as a reference medicinal product.

The application was supported by one bioequivalence study, comparing the applicant’s test product Dexamethasone 500 microgram Tablets with the ERP. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

Following start of the procedure, due to concerns with interchangeability, the ERP was replaced with the UK Reference Medicinal Product (RMP). (See also the CMDh working document on information to be submitted by the member state on the European Reference Medicinal Product)

The UK RMP is Decadron 500 microgram Tablets (PL 17736/0119; Chemidex Pharma Limited, trading as Essential Generics, UK) which was authorised in the UK following a change of ownership procedure of Decadron 500 mcg Tablets (PL 00025/5046R; Merck Sharp and Dohme Limited, UK) on 02 March 2009. Decadron 500 mcg Tablets (PL 00025/5046R; Merck Sharp and Dohme Limited, UK) was granted a Product Licence in the UK on 11 February 1987. This product was the subject of a Product Licence of Right (PLR); because Decadron 500 mcg Tablets were on the market before the Medicines Act 1968 came into force in 1971.
Given the use of a ERP in the bioequivalence study, the data provided was considered insufficient to fully support the marketing authorisation application. Additional comparative in vitro data for this product and the UK reference product were submitted to complete the data supporting the application in this case.

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

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of Dexamethasone 500 microgram Tablets outweigh the risks, and a Marketing Authorisation was granted.

II QUALITY ASPECTS

II.1 Introduction

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is available as tablets. Each tablet contains 500 micrograms of dexamethasone. The other ingredients consist of the pharmaceutical excipients lactose monohydrate, maize starch and magnesium stearate.

The finished product is supplied in polyvinyl chloride/polyvinylidene chloride/aluminium (PVC/PVdC/aluminium) blisters, in pack sizes of 30 tablets (3 blister packs; 10 tablets per blister).

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

II.2 Drug Substance

**Dexamethasone**

INN: Dexamethasone

Chemical Name: 9-fluoro-11, 17-dihydroxy-17-(2-hydroxyacetyl)-10, 13, 16-trimethyl-dodecahydro-3H-cyclopenta [a]phenanthren-3-one

Molecular formula: \( C_{22}H_{29}FO_{5} \)

Structure:

![Structure of Dexamethasone](image)

Molecular mass: 392.461 g/mol

Appearance: A white or almost white, crystalline powder

Solubility: Practically insoluble in water, sparingly soluble in anhydrous ethanol, slightly soluble in methylene chloride.

Dexamethasone is the subject of a European Pharmacopoeia monograph.
All aspects of the manufacture and control of the active substance, dexamethasone, except for the proposed packaging specifications and stability data, 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 a generic dexamethasone 500 micrograms tablet. Suitable pharmaceutical development data have been provided for this application.

Comparable in vitro dissolution profiles were provided for this product, the ERP and UK RMP. The dissolution profiles were satisfactory.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose anhydrous is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material of any kind is used during the production of lactose monohydrate. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Control of Finished Product

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

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years has been approved, with the special storage conditions ‘Do not store above 25°C.’

Suitable post approval stability commitments have been provided.

Bioequivalence/Bioavailability

One bioequivalence study, comparing the applicant’s test product with the ERP was submitted. Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Given that the bioequivalence study was considered insufficient to fully support the marketing authorisation, comparative in vitro data for this product and the UK RMP were submitted to complete the data necessary to support the application.

Comprehensive in vitro data were provided. A BCS biowaiver was not permissible, but the data provided evidence that the proposed test product formulation and method of manufacture were acceptable.
For this specific application, it was considered that the bioequivalence study provided against the ERP and the additional comparative *in vitro* data against the UK reference product, when taken together, were sufficient to fully support the marketing authorisation application.

**Conclusion**

It is recommended that a Marketing Authorisation is granted for this application for Dexamethasone 500 microgram Tablets.

**II.4 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

The SmPC, PIL and labelling 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 current labelling is presented below:
III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of dexamethasone are well-known, no new non-clinical data have been submitted and none are required.

The non-clinical overview 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 Pharmacodynamics
The pharmacodynamics profile of dexamethasone is well known and is adequately described in the applicant’s non-clinical overview.

III.3 Pharmacokinetics
The pharmacokinetic properties of dexamethasone are well known and are adequately described in the applicant’s non-clinical overview.
III.4 Toxicology
The toxicological properties of dexamethasone are well known and are adequately described in the applicant’s non-clinical overview.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Dexamethasone 500 micrograms, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction
The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
The clinical pharmacology of dexamethasone is well-known.
In support of the application, the applicant submitted the following bioequivalence study:

A single-dose, randomised, open-label, two-period, crossover bioequivalence study of the test product Dexamethasone 500 microgram Tablets with a European reference product Fortecortin 500 mcg Tablets in healthy adult volunteers.

The pharmacokinetic results for the parent compound dexamethasone are presented below:

Table 1 The main pharmacokinetic parameters for dexamethasone obtained in the bioequivalence study.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Test (Dexamethasone 500 microgram tablets /T/)</th>
<th>Reference (Fortecortin® /R/)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{last} ng/h/ml</td>
<td>303.03 ± 87.34</td>
<td>288.82 ± 72.99</td>
</tr>
<tr>
<td>AUC_{0-inf} ng/h/ml</td>
<td>333.47 ± 92.42</td>
<td>317.61 ± 75.31</td>
</tr>
<tr>
<td>C_{max} ng/ml</td>
<td>55.0 ± 12.95</td>
<td>54.5 ± 11.12</td>
</tr>
<tr>
<td>Residual area %</td>
<td>9.57 ± 2.93</td>
<td>9.43 ± 2.61</td>
</tr>
<tr>
<td>T_{max} h</td>
<td>1.42 ± 0.66</td>
<td>1.63 ± 0.61</td>
</tr>
<tr>
<td>Kel h^{-1}</td>
<td>0.19938 ± 0.03632</td>
<td>0.20396 ± 0.03912</td>
</tr>
<tr>
<td>T_{1/2} el h</td>
<td>3.58 ± 0.61</td>
<td>3.51 ± 0.64</td>
</tr>
</tbody>
</table>

Table 2 Pharmacokinetic parameters of dexamethasone

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric LS Means</th>
<th>Ratio T/R, %</th>
<th>90% Confidence Limits (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ln (AUC_{last})</td>
<td>5.65</td>
<td>5.62</td>
<td>100.53</td>
</tr>
<tr>
<td>ln (C_{max})</td>
<td>3.97</td>
<td>3.97</td>
<td>100.00</td>
</tr>
</tbody>
</table>

The 90% confidence intervals of the test/reference ratio for AUClast and Cmax lie within the acceptable limits of 80.00% to 125.00%, in line with the Guideline on the Investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).
The data show bioequivalence between the test product and ERP.

For this specific application, it was considered that the bioequivalence study against the ERP and the additional comparative *in vitro* data with the UK RMP, when taken together, were sufficient to fully support the marketing authorisation application.

**IV.3 Pharmacodynamics**
The clinical pharmacology of dexamethasone is well-known. No new pharmacodynamic data were submitted and none are required for this type of application. An adequate summary of the pharmacodynamic profile of dexamethasone has been presented in the clinical overview.

**IV.4 Clinical Efficacy**
The clinical pharmacology of dexamethasone is well-known. No new efficacy data have been submitted and none are required for this type of application. Efficacy is adequately reviewed in the clinical overview.

**IV.5 Clinical Safety**
The safety profile of dexamethasone is well known. The safety profile of dexamethasone has been adequately summarised by the Applicant in the clinical overview. No new or unexpected safety issues arose from the submitted safety data.

**IV.6 Risk Management Plan**
The MAH has submitted a risk management plan, 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 500 microgram Tablets.
Summary of Safety Concerns

**Important identified risks**
- Hypersensitivity including anaphylaxis to dexamethasone or any excipients
- Adrenal suppression (associated with long term use in children); adrenocortical insufficiency
- Risk of opportunistic infection, aggravation or masking of signs of infection; impaired immune response to vaccines
- Osteoporosis, especially in at risk patients

- Gastrointestinal ulcers or bleeding, pancreatitis and intestinal perforation
- Reduced glucose tolerance
- Vascular disorders such as hypertension, increased risk of arteriosclerosis and thrombosis, vasculitis (also as withdrawal syndrome after long-term treatment), increased capillary fragility.
- Metabolic effects such as increased potassium excretion or sodium retention with oedema
- Tendon disorders, tendinitis, and ruptured tendons
- Cataract, glaucoma or corneal ulcer
- Exacerbation or recurrence of the underlying disease, acute adrenocortical insufficiency or cortisone withdrawal syndrome on withdrawal of medication.

**Important potential risks**
- Myocardial rupture (post-infarct)
- Congestive heart failure
- Congenital abnormalities.

**Important missing information**
- Use during pregnancy and lactation

Summary table of risk minimisation measures

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Routine Risk minimisation</th>
<th>Additional risk minimisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity including anaphylaxis to dexamethasone or any excipients</td>
<td>Proposed text in SPC</td>
<td>None proposed</td>
</tr>
<tr>
<td>Adrenal suppression (associated with long term use in</td>
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</tr>
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</tr>
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<tr>
<td>Congenital abnormalities</td>
<td>Proposed text in SPC</td>
<td>None proposed</td>
</tr>
<tr>
<td>Use during pregnancy and lactation</td>
<td>Proposed text in SPC</td>
<td>None proposed</td>
</tr>
</tbody>
</table>
Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

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. The language used for the purpose of user testing the pack leaflet was English.

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 AND RECOMMENDATION

QUALITY
The important quality characteristics of Dexamethasone 500 microgram Tablets 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. As the pharmacokinetics, pharmacodynamics and toxicology of dexamethasone are well-known, no additional data were required.

EFFICACY
The published literature supports the efficacy of the product in the proposed indications and posology. The efficacy of dexamethasone is well-known.

The bioequivalence study with the ERP and the additional comparative in vitro data with the UK RMP, when taken together, were considered sufficient to fully support the marketing authorisation application.

SAFETY
The safety profile of dexamethasone is well known and no additional safety data were required. No new or unexpected safety concerns arose from the application.

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 balance is therefore considered to be positive.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.
Dexamethasone 500 microgram Tablets

PL 42701/0001

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Marketing Authorisation application on 13 November 2013.
2. Following standard checks and communication with the applicant the MHRA considered the application valid on 18 November 2013.
3. Following assessment of the application, the MHRA requested further information relating to the dossier on 15 April 2014 and 11 September 2014.
4. The applicant responded to the MHRA’s requests, providing further information on the dossier on 20 June 2014 and 08 October 2014.
5. The application was granted on 26 November 2014.
### STEPS TAKEN AFTER THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
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