Public Assessment Report

Dexamethasone 2mg Tablets

(dexamethasone)

UK Licence No.: PL 42701/0002

Trotwood Pharma Limited
Lay Summary
Dexamethasone 2mg Tablets
(Dexamethasone)

This is a summary of the Public Assessment Report (PAR) for Dexamethasone 2mg Tablets (PL 42701/0002). It explains how Dexamethasone 2mg Tablets were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Dexamethasone 2mg Tablets.

For practical information about using Dexamethasone 2mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Dexamethasone 2mg Tablets and what are they used for?
The application for Dexamethasone 2mg Tablets is a hybrid application. This means that Dexamethasone 2mg Tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Dexamethasone 500 microgram Tablets (PL 17736/0119), containing a different strength of the same active substance dexamethasone.

Dexamethasone 2mg Tablets are used for the following illnesses and conditions:
- 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 excessive 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 2mg Tablets work?
Dexamethasone Tablets belong to a group of medicines called steroids. Their full name is corticosteroids. These 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. Dexamethasone tablets reduce this inflammation, which could otherwise go on making the condition worse.

How are Dexamethasone 2mg Tablets used?
Dexamethasone 2mg Tablets are taken by mouth. The whole tablet should be swallowed with plenty of water, with or immediately after a meal to prevent an upset stomach.
The tablets must be taken regularly as advised by a doctor to obtain the maximum benefit.

Dexamethasone 2mg Tablets can only be obtained with a prescription.

**What benefits of Dexamethasone 2mg Tablets have been shown in studies?**
The applicant has referred to the study that was submitted in support of an application for Dexamethasone 500 microgram tablets (PL 42701/0001). In this application, studies were limited to tests to determine that Dexamethasone 500 microgram tablets are bioequivalent to the reference medicine Dexamethasone 500 microgram tablets (Chemidex Pharma Limited, trading as Essential Generics, UK). Two medicines are bioequivalent when they produce the same level 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 of Dexamethasone 2mg Tablets?**
Like all medicines, Dexamethasone 2mg Tablets can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Dexamethasone 2mg Tablets, see section 4 of the package leaflet available on the MHRA website.

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

**Why was Dexamethasone 2mg Tablets approved?**
The MHRA decided that the benefits of Dexamethasone 2mg Tablets outweigh the identified risks and it was recommended that it be approved for use.

**What measures are being taken to ensure the safe and effective use of Dexamethasone 2mg Tablets?**
A risk management plan (RMP) has been developed to ensure that Dexamethasone 2mg Tablets is 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 2mg 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.

**Other information about Dexamethasone 2mg Tablets**
A Marketing Authorisation was granted in the UK on 25 November 2016.

For more information about taking Dexamethasone 2mg Tablets, read the package leaflet, or contact your doctor or pharmacist. The full PAR for Dexamethasone 2mg Tablets follows this summary.

This summary was last updated in December 2016.
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I Introduction
The Medicines and Healthcare products Regulatory Agency (MHRA) granted Trotwood Pharma Limited a Marketing Authorisation for the medicinal product Dexamethasone 2mg Tablets (PL 42701/0002) on 25 November 2016. This is a prescription only medicine (POM), 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, 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.
- Rheumatic disorders: Rheumatoid arthritis.
- Skin disorders: Pemphigus vulgaris.

This application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application. The applicant cross refers to Dexamethasone 500 microgram Tablets (PL 17736/0119; Chemidex Pharma Limited, trading as Essential Generics, UK), previously known as Decadron 500 mcg Tablets which was authorised in the UK following a change of ownership procedure of Decadron 500 microgram Tablets (PL 00025/5046R; Merck Sharp and Dohme Limited, UK) on 02 March 2009. Decadron 500 microgram (PL 00025/5046R) 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 microgram Tablets were on the market before the Medicines Act 1968 came into force in 1971.

Dexamethasone 2mg Tablets contain the active ingredient dexamethasone which is a glucocorticoid. It possesses the actions and effects of other basic glucocorticoids, and is among the most active members. 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 cortisol), which also have salt retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs, including dexamethasone, are used primarily for their potent anti-inflammatory effects in disorders of many organ systems.

No new bioequivalence data was submitted with this application. The applicant currently holds a Marketing Authorisation for Dexamethasone 500 mcg tablets (PL 42701/0001). In support of the application for Dexamethasone 2 mg tablets (PL 42701/0002), the results of the bioequivalence study that was submitted for Dexamethasone 500 mcg tablets (PL 42701/0001) were provided. This study compared the pharmacokinetics of the test product Dexamethasone 500 microgram tablets with the European reference product Fortecortin 500 micrograms tablets (Merck Serono GmbH) in healthy adult volunteers. The bioequivalence study was carried out in accordance with good Clinical Practice (GCP). Additional in vitro data for this product were provided demonstrating comparability with the UK reference product, Decadron (PL 42701/0001). The applicant successfully established the linearity of the pharmacokinetics of orally administered dexamethasone between a 0.5 mg and 2 mg dose. The criteria set out in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) for establishing a strength biowaiver between the already approved Dexamethasone 500 mcg Tablets (PL 42701/0001) and the proposed Dexamethasone 2 mg Tablets (PL 42701/0002) were met.

Therefore, for this specific application, the bioequivalence study with the already authorised product, Dexamethasone 500 mcg Tablets, in combination with extensive in vitro data, support a biowaiver for the additional strength, Dexamethasone 2 mg Tablets (PL 42701/0002).

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

A summary of the pharmacovigilance system and a detailed risk management plan have been provided with this application and these are satisfactory.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Dexamethasone 2mg Tablets outweigh the risks and a Marketing Authorisation were granted.
II QUALITY ASPECTS

II.1 Introduction
The product is a round, white, flat tablet, 6 mm in diameter, debossed with D2 on one side. Each tablet contains 2 milligrams dexamethasone, as active ingredient.

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, maize starch and magnesium stearate. All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

The finished product is packaged in polyvinylchloride (PVC)/polyvinylidenechloride (PVdC)/aluminium foil blister packs, containing 50 tablets per pack.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
INN: Dexamethasone
Structural formula:

\[
\text{Molecular formula: } \text{C}_{22}\text{H}_{29}\text{FO}_5 \\
\text{Molecular mass: } 392.5 \text{ g/mol} \\
\text{Appearance: } \text{White or almost white, crystalline powder.} \\
\text{Solubility: } \text{Dexamethasone is sparingly soluble in anhydrous ethanol, practically insoluble in water and slightly soluble in methylene chloride.}
\]

Dexamethasone is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, dexamethasone, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.
II.3  Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe and efficacious tablets that are equivalent to the reference product Decadron 500 microgram Tablets (Chemidex Pharma Limited). Suitable pharmaceutical development data have been provided for this application.

Comparative in vitro dissolution profiles were provided for this product, the European reference product and the UK reference product. The dissolution profiles were satisfactory.

Manufacture of the product
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 pilot-scale batch size and shown satisfactory results. The Marketing Authorisation holder has committed to perform process validation studies on consecutive full-scale production batches.

Finished Product Specifications
The finished product specification proposed is acceptable. The test methods have been described that have been adequately validated. 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. The data from these studies support a shelf-life of 2 years with storage conditions “Do not store above 25°C” and “Store in the original package in order to protect from light”.

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

II.4  Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III  NON-CLINICAL ASPECTS
III.1  Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of dexamethasone are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical data on the pharmacology, pharmacokinetics and toxicology of dexamethasone.
III.2 **Pharmacology**
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 **Pharmacokinetics**
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 **Toxicology**
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 **Ecotoxicity/environmental risk assessment (ERA)**
Since this product is intended for generic substitution, its use will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 **Discussion on the non-clinical aspects**
There are no objections to the approval of this application from a non-clinical viewpoint.
IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of dexamethasone is well-known. No new pharmacodynamics or pharmacokinetic data are provided or were required for this particular application. The Applicant proposed a biowaiver for this additional strength, Dexamethasone 2 mg Tablet supported by extensive in vitro data and the bioequivalence study submitted for the currently approved Dexamethasone 500 microgram tablets (PL 42701/0001; Trotwood Pharma Limited).

No new efficacy or safety studies have been performed 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.

IV.2 Pharmacokinetics
No new pharmacokinetic data were submitted in support of this application. The bioequivalence study submitted in support of Dexamethasone 500 microgram Tablets (PL 42701/0001) was provided as supportive data along with extensive in vitro data.

Based on the established linearity of the pharmacokinetics of orally administered dexamethasone between a 0.5 mg and 2 mg dose, a strength biowaiver between the already approved Dexamethasone 500 mcg Tablets (PL 42701/0001) and the proposed Dexamethasone 2 mg Tablets was accepted.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for applications of this type.

IV.5 Clinical safety
No new safety data were submitted and none were required for this application.
IV.6 Risk Management Plan (RMP)
The Marketing Authorisation Holder (MAH) 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 2mg Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

<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 SmPC</td>
<td>None proposed</td>
</tr>
<tr>
<td>Adrenal suppression (associated with long term use in children); adrenocortical insufficiency</td>
<td>Proposed text in SmPC</td>
<td>None proposed</td>
</tr>
<tr>
<td>Risk of opportunistic infection, aggravation or masking of signs of infection; impaired immune response to vaccines</td>
<td>Proposed text in SmPC</td>
<td>None proposed</td>
</tr>
<tr>
<td>Osteoporosis, especially in at risk patients</td>
<td>Proposed text in SmPC</td>
<td>None proposed</td>
</tr>
<tr>
<td>Gastrointestinal ulcers or bleeding, pancreatitis and intestinal perforation</td>
<td>Proposed text in SmPC</td>
<td>None proposed</td>
</tr>
<tr>
<td>Reduced glucose tolerance</td>
<td>Proposed text in SmPC</td>
<td>None proposed</td>
</tr>
<tr>
<td>Vascular disorders such as hypertension, increased risk of atherosclerosis and thrombosis, vasculitis (also as withdrawal syndrome after long-term treatment), increased capillary fragility.</td>
<td>Proposed text in SmPC</td>
<td>None proposed</td>
</tr>
<tr>
<td>Metabolic effects such as increased potassium excretion or sodium retention with oedema</td>
<td>Proposed text in SMPC</td>
<td>None proposed</td>
</tr>
<tr>
<td>Tendon disorders, tendinitis, and ruptured tendons</td>
<td>Proposed text in SmPC</td>
<td>None proposed</td>
</tr>
<tr>
<td>Cataract, glaucoma or corneal ulcer</td>
<td>Proposed text in SmPC</td>
<td>None proposed</td>
</tr>
<tr>
<td>Exacerbation or recurrence of the underlying disease, acute adrenocortical insufficiency or cortisone withdrawal syndrome on withdrawal of medication.</td>
<td>Proposed text in SmPC</td>
<td>None proposed</td>
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<tr>
<td>Myocardial rupture (post-infarct)</td>
<td>Proposed text in SmPC</td>
<td>None proposed</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Proposed text in SmPC</td>
<td>None proposed</td>
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<tr>
<td>Congenital abnormalities</td>
<td>Proposed text in SmPC</td>
<td>None proposed</td>
</tr>
<tr>
<td>Use during pregnancy and lactation</td>
<td>Proposed text in SmPC</td>
<td>None proposed</td>
</tr>
</tbody>
</table>
Routine pharmacovigilance and routine risk minimisation measures are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects
There are no objections to the approval of this application from a clinical viewpoint.

The grant of a Marketing Authorisation is recommended 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 PIL 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, benefit/risk assessment and recommendation
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with dexamethasone is considered to have demonstrated the therapeutic value of the compounds. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Dexamethasone 2mg Tablets is presented below:
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Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitment)

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<th>Scope</th>
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