Public Assessment Report

Decentralised Procedure

Prednisolone Dompé 1.0 mg/ml oral solution

Prednisolone sodium phosphate

Procedure No: UK/H/5254/001/DC

UK Licence No: PL 12529/0002

Dompé s.p.a.
LAY SUMMARY

On 19 August 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation to Dompé s.p.a for the medicinal product Prednisolone Dompé 1.0 mg/ml oral solution (PL 12529/0002; UK/H/5254/001/DC). This is a prescription-only medicine (POM).

Prednisolone Dompé 1.0 mg/ml oral solution contains the active ingredient, prednisolone (as prednisolone sodium phosphate ester), which belongs 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 prednisolone) is an effective way to treat various illnesses involving inflammation in the body. Prednisolone Dompé 1.0 mg/ml oral solution reduces this inflammation, which could otherwise go on making these conditions worse. Prednisolone Dompé 1.0 mg/ml oral solution must be taken regularly to get the maximum benefit from it.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Prednisolone Dompé 1.0 mg/ml oral solution outweigh the risks, and a Marketing Authorisation was granted.
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Module 1
Information about the initial procedure

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Prednisolone Dompé 1.0 mg/ml oral solution</th>
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<tr>
<td>Type of Application</td>
<td>Well-established use, Article 10a</td>
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<tr>
<td>Active Substance</td>
<td>Prednisolone sodium phosphate</td>
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<tr>
<td>Form</td>
<td>Oral solution</td>
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<tr>
<td>Strength</td>
<td>Oral solution; 1 mg/ml of prednisolone (as prednisolone sodium phosphate)</td>
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<td>Note: Presentation as 5ml single dose units</td>
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<td>MA Holder</td>
<td>Dompé s.p.a</td>
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<td></td>
<td>Via Campo di Pile</td>
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<td></td>
<td>67100 L’Aquila - Italy</td>
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<td>Reference Member State (RMS)</td>
<td>UK</td>
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<tr>
<td>Concerned Member State (CMS)</td>
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<td>Procedure Number</td>
<td>UK/H/5254/001/DC</td>
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<tr>
<td>Timetable</td>
<td>Day 210 – 21 July 2013</td>
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Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4

Labelling

The Marketing Authorisation Holder has submitted a text version only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING (CARTON)

1. NAME OF THE MEDICINAL PRODUCT

Prednisolone Dompé 1.0 mg/ml oral solution

Prednisolone sodium phosphate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of the oral solution contains 1 mg of prednisolone (as sodium phosphate).
Each vial of 5 ml solution contains 5 mg of prednisolone (as sodium phosphate)

3. LIST OF EXCIPIENTS

Contains: sucrose, glycerol and sodium. See the leaflet for further information.
Sucrose, glycerol, Edetate disodium (EDTA), Disodium phosphate anhydrous, Sodium dihydrogen phosphate monohydrate, Vanilla/cream flavour, Honey flavour, Masking flavour, Purified water.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution
5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Expiry date (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Store in the original package.
Once opened, in case of administration of partial doses, the opened container must be discarded once the required dose is removed.
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

   Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

    Dompé spa  
    Via Campo di Pile  
    67100 L’Aquila - Italy

12. **MARKETING AUTHORISATION NUMBER(S)**

13. **BATCH NUMBER**

    Batch

14. **GENERAL CLASSIFICATION FOR SUPPLY**

    POM

15. **INSTRUCTIONS ON USE**

    Use only as directed by the physician.

16. **INFORMATION IN BRAILLE**
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS (POUCH)

1. NAME OF THE MEDICINAL PRODUCT

Prednisolone Dompé 1.0 mg/ml oral solution
Prednisolone sodium phosphate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Dompé spa
Via Campo di Pile
67100 L’Aquila - Italy

3. EXPIRY DATE

NOT APPLICABLE AS ALREADY STATED IN THE OUTER PACKAGING AND ON THE VIAL.

4. BATCH NUMBER

NOT APPLICABLE AS ALREADY STATED IN THE OUTER PACKAGING AND ON THE VIAL.

5. OTHER

For oral use

Do not store above 30°C. Store in the original package.
Once the single container is opened: in case of administration of partial doses, the opened container must be discarded once the required dose is removed.
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS (VIAL)

1. **NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

   Prednisolone Dompé 1.0 mg/ml oral solution

2. **METHOD OF ADMINISTRATION**

3. **EXPIRY DATE**

   Expiry date (MM/YYYY)

4. **BATCH NUMBER**

   Batch

5. **CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

   5 ml

6. **OTHER**
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the UK and Italy considered that the application for Prednisolone Dompé 1.0 mg/ml oral solution (PL 12529/0002; UK/H/5254/001/DC) could be approved. The product is a prescription-only medicine (POM) and it is indicated for the following:

- Rheumatological disorders and connective tissue diseases such as:
  - rheumatoid arthritis (for primary chronic disease and maintenance therapy);
  - systemic lupus erythematosus (non-organ threatening disease);
  - mild-moderate juvenile dermatomyositis.
- Severe or debilitating allergic conditions, not treatable in a conventional manner such as:
  - bronchial asthma in children;
  - bronchial asthma in adults (for maintenance therapy).
- Sarcoidosis in children and for maintenance therapy in adults.
- Acquired haemolytic anaemia (autoimmune, for maintenance therapy).

Prednisolone Dompé 1.0 mg/ml oral solution contains the active ingredient prednisolone (prednisolone sodium phosphate), which belongs to the pharmacological class of corticosteroids with predominantly glucocorticoid properties possessing anti-inflammatory and immunosuppressive effects. Prednisolone diffuses across the cell membrane and forms complexes with specific cytoplasmic receptors. The complexes enter the cell nucleus, bind to DNA, modifying gene transcription and, consequently, stimulating the synthesis of some genes and inhibiting others. Prednisolone is the active metabolite of prednisone.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Italy as Concerned Member State (CMS). The application was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use. Prednisolone, as such, or in the form of ester derivatives (sodium phosphate, sodium metasulphobenzoate, acetate etcetera), has been available on the market in the EEA countries for decades, mostly as solid oral presentations (capsules or tablets) but also as soluble oral presentations (that is, effervescent tablets, orosoluble tablets, and oral solution) in some EEA countries, as well as outside of the EEA.

Bibliographic literature data on prednisolone/prednisone products have been submitted to support this application. No new non-clinical or clinical studies were conducted for this application, which is acceptable given that this is a bibliographic application for a product containing an active ingredient of well-established use.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 21 July 2013. After a subsequent national phase, a licence was granted in the UK on 19 August 2013.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Prednisolone Dompé 1.0 mg/ml oral solution</th>
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<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Prednisolone sodium phosphate</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Glucocorticoids (ATC code: H02AB06)</td>
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<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Oral solution; 1 mg/ml of prednisolone (as prednisolone sodium phosphate)</td>
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<tr>
<td>Name and address of the authorisation holder</td>
<td>Dompé s.p.a.</td>
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<td>Via Campo di Pile</td>
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<td>67100 L’Aquila</td>
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III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Prednisolone sodium phosphate
Chemical Name: 11β,17-dihydroxy-3,20-dioxpregna-1,4-dien-21-yl disodium phosphate
Molecular formula: C_{21}H_{27}Na_{2}O_{8}P
Structure:

![Chemical Structure Image]

Molecular mass: 484.39
Appearance: White or almost white crystalline powder
Solubility: Freely soluble in water, very soluble in alcohol and practically insoluble in ether.

Prednisolone sodium phosphate is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been described adequately and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been validated appropriately and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

**MEDICINAL PRODUCT**

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients sucrose, glycerol, edetate disodium (EDTA), disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, honey flavour, vanilla/cream flavour, masking flavour and purified water. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of honey flavour, vanilla/cream flavour and masking flavour, which are controlled to suitable in-house specifications. Certificates of Analysis have been provided for all excipients, showing compliance with their respective specifications.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**

The objective of the development programme was to formulate a safe, efficacious, stable, new liquid formulation of prednisolone for oral use with characteristics such as to support use of the product in the target population, including the pediatric setting.

Suitable pharmaceutical development data have been provided for this application.

**Manufacturing Process**

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 with full production-scale batches and has shown satisfactory results.

**Control of Finished Product**

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

**Container-Closure System**

The finished product is packaged in single-dose polyethylene containers containing 5 ml of oral solution, grouped in strips of five containers. Each strip is packaged in a polyethylene terephthalate/aluminium/polyethylene (PET/Al/PE) over-pouch. Each unit carton contains two over-pouches (ten single-doses), a Patient Information Leaflet and a measuring spoon (dosing 3.75 ml, 2.5 ml and 1.25 ml, corresponding to partial doses).

The product is available in a pack size of 10 single-dose containers.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidance concerning materials in contact with foodstuff.
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 2 years has been approved for the unopened product, with the storage instructions ‘Do not store above 30°C. Store in the original package.’

Once opened, in case of administration of partial doses, the opened container must be discarded once the required dose is removed.

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

Bioequivalence/Bioavailability
A bioequivalence study was not necessary to support this type of application.

Summary of Product Characteristics (SmPC), Product Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are satisfactory from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), 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 the leaflet contains.

Marketing Authorisation Application (MAA) Form
The MAA form is satisfactory from a pharmaceutical perspective.

Expert Report (Quality Overall Summary)
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of prednisolone are well-known, no new non-clinical data have been submitted and none are required.

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.

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. This was an application for a product containing an active ingredient of well-established use; no increase in environmental burden is anticipated. In addition, the Marketing Authorisation Holder has calculated the predicted environmental concentration (PEC) in surface water to be of 0.0005 microgram/L; which is below the PEC action limit of 0.01 microgram/L.

The grant of a Marketing Authorisation is recommended.
III.3 CLINICAL ASPECTS

Clinical Pharmacology
No new clinical pharmacology data have been submitted and none are required for this type of application. The clinical pharmacology of prednisolone is well-known.

Efficacy
No new efficacy data have been submitted and none are required for this type of application. The clinical efficacy of prednisolone is well-established.

Safety
No new safety data were supplied or required for this bibliographic application. Safety is adequately reviewed in the clinical overview. The safety profile of prednisolone is well-known.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are acceptable from a clinical perspective. The PIL is consistent with the details in the SmPC and in line with the current guidance. The labelling is in line with the current guidance.

Clinical Expert Report (Clinical Overview)
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the MAH, fulfils the requirements and provides adequate evidence that the MAH 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.

Suitable justification has been provided for not submitting a Risk Management Plan for this application.

Conclusion
The grant of a Marketing Authorisation is recommended.

IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Prednisolone Dompé 1.0 mg/ml oral solution 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 and none are required for this type of application. A non-clinical overview has been provided by an appropriately qualified person and consists of a review of the published literature.

EFFICACY
No new clinical data were submitted and none were required for this type of application.

The published literature supports the efficacy of this product in the proposed indications. The efficacy of prednisolone is well-known. The presented evidence for well-established use of the active substance is sufficient.
SAFETY
The safety profile of prednisolone is well-known. The literature review identified no new or unexpected safety issues or concerns.

PRODUCT LITERATURE
The approved SmPC is satisfactory. The PIL and labelling are satisfactory, and consistent with the approved SmPC.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Prednisolone is a well-known active substance. Extensive clinical experience with prednisolone is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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