Prednisolone 25mg Tablets

PL 41830/0026

UKPAR

TABLE OF CONTENTS

PREDNISOLONE 25MG TABLETS

PL 41830/0026

LAY SUMMARY

This is a summary of the public assessment report (PAR) for Prednisolone 25mg Tablets (PL 41830/0026). It explains how Prednisolone 25mg Tablets 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 Prednisolone 25mg Tablets.

For practical information about using Prednisolone 25mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Prednisolone 25mg Tablets and what are they used for?
Prednisolone 25mg Tablets is a 'generic medicine'. This means that Prednisolone 25mg Tablets are similar to a 'reference medicine' already authorised in the European Union (EU) called Precortisyl Forte/Prednisolone 25mg Tablets.

Prednisolone 25mg Tablets are used to treat illnesses (sometimes called systemic autoimmune diseases) which cause inflammation of the skin, muscles or joints. These include rheumatic fever and systemic lupus erythematosus (SLE). Prednisolone 25mg Tablets are also used to treat blood problems (such as anaemia and leukaemia), skin problems, kidney problems and stomach problems (such as ulcerative colitis).

How do Prednisolone 25mg Tablets work?
The tablets belong to a group of medicines called the glucocorticoids, which belong to a class of chemicals called the corticosteroids. Corticosteroids occur naturally in the body, and help to maintain health and well-being. Taking extra corticosteroids (such as prednisolone) is an effective way to treat various illnesses involving inflammation in the body. Prednisolone works by reducing this inflammation. It also stops reactions known as autoimmune reactions. These reactions happen when your body's immune system attacks the body itself and causes damage.

How are Prednisolone 25mg Tablets used?
Prednisolone 25mg Tablets should be swallowed with a glass of water. The recommended starting dose is three tablets, taken together each morning. A doctor may change the dose if the patient has been taking prednisolone for a long time, becomes ill or needs to have an operation. The lowest dose to produce an acceptable result should be given; when it is possible to reduce the dose, this should be done gradually in stages.

The medicine can only be obtained with a prescription.

What benefits of Prednisolone 25mg Tablets have been shown in studies?
Because Prednisolone 25mg Tablets is a generic medicine, studies in patients have been limited to tests to determine that this medicine is bioequivalent to the reference medicine, Precortisyl Forte/Prednisolone 25mg Tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Prednisolone 25mg Tablets?
Because Prednisolone 25mg Tablets is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as those of the reference medicine.

Why are Prednisolone 25mg Tablets approved?
It was concluded that, in accordance with EU requirements, Prednisolone 25mg Tablets have been shown to have comparable quality and to be bioequivalent to Precortisyl Forte/Prednisolone 25mg Tablets. Therefore, the MHRA decided that, as for Precortisyl Forte/Prednisolone 25mg Tablets, the benefits of this medicine are greater than its risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Prednisolone 25mg Tablets?
A Risk Management Plan has been developed to ensure Prednisolone 25mg 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 Prednisolone 25mg 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 Prednisolone 25mg Tablets
The Marketing Authorisation for Prednisolone 25mg Tablets was granted in the UK on 18 August 2014.

This summary was last updated in October 2014.

The full PAR for Prednisolone 25mg Tablets follows this summary.

PREDNISOLONE 25MG TABLETS

PL 41830/0026

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation for the medicinal product Prednisolone 25mg Tablets (PL 41830/0026) to NRIM Limited on 18 August 2014. This prescription only medicine (POM) is used for the treatment of systemic autoimmune diseases (such as systemic lupus erythematosus, acute rheumatic fever), haematological disorders (such as acute granulocytic leukaemia, acute monocytic leukaemia, chronic lymphocytic leukaemia, thrombocytopenia and haemolytic anaemia) as well as the conditions ulcerative colitis, pemphigus and non-inflammatory nephropathy.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, with the applicant claiming that the proposed product was a generic medicinal product of the reference product Precortisyl Forte/Prednisolone 25mg Tablets. The reference product was originally authorised on 20 May 1980 to Roussel Laboratories (PL 00109/0091) as an additional strength line extension from Precortisyl tablets 1mg (PL 0109/5033R) and Precortisyl tablets 5mg (PL 0109/5034R), which were already authorised to Roussel Laboratories. Following a change of ownership on 15 April 1998 the reference product was authorised to Hoechst Marion Roussel Ltd (PL 13402/0090); this was followed by a change of ownership on 8 March 2002 in which the product was authorised to Aventis Pharma Limited (PL 04425/0333) and a subsequent change of ownership on 19 January 2009 in which the reference product was authorised to Winthrop Pharmaceuticals (PL 17780/0309). Precortisyl Forte/Prednisolone 25mg Tablets has been authorised for more than 10 years and therefore is suitable as a reference product.

Prednisolone is a synthetic corticosteroid with predominantly glucocorticoid properties. Due to its potent anti-inflammatory and immunosuppressive actions it is widely used in a broad range of indications. Prednisolone exceeds hydrocortisone with respect to glucocorticoid activity and is approximately three times more potent on a weight for weight basis than hydrocortisone; however, it is considerably less potent than hydrocortisone in mineralocorticocoid activity which reduces its side-effect profile. Orally administered prednisolone is readily absorbed by the gastrointestinal tract and is an active form. In contrast, orally ingested prednisone requires conversion by hepatic metabolism to prednisolone.

Prednisolone is used over a wide dose range. Low dose corticosteroid therapy is considered to include doses of prednisolone up to 10mg per day and is most commonly prescribed at 5 - 7.5mg per day. The dose has to be titrated to individual need and is highly variable, depending on the nature and severity of the disease. There is no absolute maximum dosage; however, intensity and frequency of adverse events rises with increasing dose. In the initial treatment of acute illnesses daily doses of 75mg or more may be needed with the aim of gradual dose reduction to the minimum effective dose, once control of the disease has been achieved. In the case of prolonged treatment, dose reduction is accomplished by gradual tapering of dose to allow the hypothalamo-pituitary-adrenal axis to recover; furthermore, the dose of prednisolone may need to be temporarily increased during intercurrent illness and in periods of physical or psychological stress.

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

With the exception of the bioequivalence/bioavailability studies no clinical studies were conducted, which is acceptable given that the application was based on the product being a generic medicinal product of the reference product, which has been licensed for over 10 years.

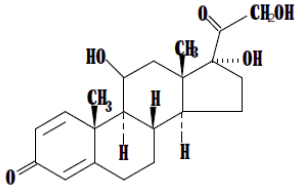
A bioequivalence study was performed which compared the pharmacokinetics of Prednisolone 25mg Tablets with those of Precortisyl Forte/Prednisolone 25mg Tablets (Winthrop Pharmaceuticals). The study was carried out in accordance with Good Clinical Practice (GCP).

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.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE: **PREDNISOLONE**

INN: Prednisolone
Chemical name: 11β, 17, 21-trihydroxypregna-1, 4-diene-3, 20-dione
Molecular formula: $C_{21}H_{28}O_5$
Molecular mass: 360.4g/mol
Structure:



General properties: A white or almost white crystalline powder, very slightly soluble in water, soluble in alcohol and methanol, sparingly soluble in acetone and slightly soluble in methylene chloride.

MEDICINAL PRODUCT: **PREDNISOLONE 25MG TABLETS**

Description and composition
The white to off-white, round, bevel-edged tablets have a break line on one side and 'P25' engraved on the other side. Each tablet contains 25mg of prednisolone and the excipients lactose monohydrate, pregleatinised starch, talc and magnesium stearate.

All excipients comply with their European Pharmacopoeia monographs.

A statement of BSE/TSE safety has been presented, certifying that the milk used for the manufacture of lactose is appropriately sourced.

Pharmaceutical Development
The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent product that could be considered a generic medicinal product of the reference product, Precortisyl Forte/Prednisolone 25mg Tablets. A satisfactory account of the pharmaceutical development has been provided.

Manufacture
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 pilot scale batches of the finished product and the results are satisfactory.

Control of medicinal product
The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The finished product is packaged in aluminium-PVC blister packs. Pack sizes of 28, 56 or 84 tablets have been authorised, although not all pack sizes may be marketed.

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 foodstuffs.

Stability
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 24 months when the storage precautions "Do not store above 25ºC" and "Store in the original package in order to protect from light" are applied.

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

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.

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

Quality Overall Summary
The quality overall summary is 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.

NON-CLINICAL ASSESSMENT

As the pharmacodynamic, pharmacokinetic and toxicological properties of prednisolone are well-known, no non-clinical studies are required and none have been provided.

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

Suitable justification has been provided for the non-submission of an Environmental Risk Assessment. As this product is intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

There are no objections to the approval of this product from a non-clinical viewpoint.

CLINICAL ASSESSMENT

Clinical pharmacology

In support of this application, the Marketing Authorisation Holder has submitted the following bioequivalence study:

An open label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period crossover oral bioequivalence study of Prednisolone 25mg Tablets (NRIM Limited UK) with Prednisolone 25mg Tablets (Winthrop Pharmaceuticals) in healthy, adult male human subjects under fed conditions.

Subjects were given a high fat, high calorie breakfast 30 minutes prior to ingestion of study drug. Subjects received a single 25mg tablet of either test or reference prednisolone at the start of study periods 1 and 2, separated by a wash-out period of seven days. Blood samples were collected for analysis pre-dose and at intervals up to 24 hours post-dose.

Thirty two subjects were enrolled and all completed the study. Data from all subjects were included in the final pharmacokinetic and statistical analysis.

Pharmacokinetic and statistical parameters for prednisolone are summarised in the table below.

Parameters (Units)	Ratio of Geometric Least Squares Means			Intra Subject CV %	90% Confidence Limits (%)	Power %
	Test product (T)	Reference product (R)	(T/R) %		(T vs. R)	
C_{max} (ng/mL)	396.317	388.071	102.1	12.9	96.70 –107.85	100.0
AUC_{0-t} (ng. hr/mL)	2741.291	2674.230	102.5	6.3	99.79 –105.30	100.0

The 90% confidence intervals for the ratios between T and R products of least squares means for C_{max} and $AUC_{(0-t)}$ were, respectively, 96.70 – 107.85% and 99.79 – 105.30%. Confidence intervals were within the acceptance range of 85.00 – 125.00%. In conclusion, Prednisolone 25mg Tablets (NRIM Limited UK) can be concluded to be bioequivalent to Prednisolone 25mg Tablets (Winthrop Pharmaceuticals).

Efficacy

No new data on efficacy have been submitted and none are required for this type of application.

Safety

With the exception of the data submitted during the bioequivalence study, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the bioequivalence study.

Pharmacovigilance system
The pharmacovigilance system as described by the applicant fulfils the legislative requirements. A risk management plan has been submitted in accordance with the EU RMP template and is acceptable.

Expert report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Summary of Product Characteristics (SmPC)
This is consistent with the SmPC for the reference product and is satisfactory.

Patient Information Leaflet (PIL)
This is consistent with that for the reference product and is satisfactory.

Labelling
This is satisfactory

Marketing authorisation application (MAA) form
The MAA form is satisfactory from a clinical perspective.

Conclusion
The grant of a marketing authorisation is recommended for this application.

OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY

The important quality characteristics Prednisolone 25mg 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 and none are required for this type of application.

CLINICAL

Bioequivalence has been demonstrated between the applicant's product and Precortisyl Forte/Prednisolone 25mg Tablets.

No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant's product and the reference product. 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.

PREDNISOLONE 25MG TABLETS

PL 41830/0026

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation application on 19 September 2013.

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 8 November 2013.

3 Following assessment of the application the MHRA requested further information relating to the dossier on 14 February 2014, 7 July 2014 and 23 July 2014.

4 The applicant responded to the MHRA's requests, providing further information on 8 May 2014, 14 July 2014 and 31 July 2014.

5 The application was granted on 18 August 2014.

STEPS TAKEN AFTER INITIAL AUTHORISATION – SUMMARY

Not applicable

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.

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.

LABELLING

Blister:

Carton:


Prednisolone
25mg Tablets
56 Tablets
NRIM
BN:
Exp:
Prednisolone
25mg Tablets
56 Tablets
NRIM
Prednisolone
25mg Tablets
56 Tablets
NRIM
Each tablets contains 25mg of prednisolone.
Also contains lactose.
For oral administration.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 25ºC. Store in the original package in order to protect from light.
Use as directed by your physician.
Affix dispensing label here
5 060090 471796
Prednisolone
25mg Tablets
56 Tablets
NRIM
POM
PL 41830/0026
PL Holder:
NRIM Limited
Unit 15 Moorcroft, Harlington Road
Hillingdon, UB8 3HD, UK