Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Prednisolone 2.5mg Tablets
Prednisolone 5mg Tablets
Prednisolone 10mg Tablets
Prednisolone 20mg Tablets
Prednisolone 25mg Tablets
Prednisolone 30mg Tablets

(Prednisolone)

Procedure No: UK/H/6012/001-006/DC

UK Licence Number: PL 24668/0296-301

Caduceus Pharma Ltd.

LAY SUMMARY

Prednisolone 2.5mg, 5mg, 10mg, 20mg, 25mg and 30mg Tablets
(prednisolone, tablet, 2.5mg, 5mg, 10mg, 20mg, 25mg and 30mg).

This is a summary of the Public Assessment Report (PAR) for Prednisolone 2.5mg, 5mg, 10mg, 20mg, 25mg and 30mg Tablets (PL 24668/0296-301; UK/H/6012/001-006/DC). It explains how Prednisolone 2.5mg, 5mg, 10mg, 20mg, 25mg and 30mg 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 2.5, 5mg, 10mg, 20mg, 25mg and 30mg Tablets.

The products will be collectively referred to as Prednisolone Tablets throughout the remainder of this public assessment report (PAR).

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

What are Prednisolone Tablets and what are they used for?
Prednisolone 2.5 mg, 5mg and 10mg Tablets are 'generic medicines'. This means that Prednisolone 2.5 mg, 5mg and 10mg Tablets are similar to 'reference medicines' already authorised in the European Union (EU) called Prednisolon Pfizer 2.5 mg, 5 mg and 10 mg (Pfizer AB, Sweden).

Prednisolone 20mg, 25mg and 30mg Tablets are 'hybrid generic medicines'. This means that they are similar to a reference medicine containing the same active substance, but are available at a higher strength (20mg, 25mg and 30mg tablets instead of 2.5 mg, 5 mg and 10 mg tablets as the reference medicine).

The reference medicine for Prednisolone 20mg Tablets is Prednisolon Pfizer 10 mg (Pfizer AB, Sweden).

The reference medicine for Prednisolone 25mg Tablets is Prednisolon Pfizer 2.5 mg (Pfizer AB, Sweden).

The reference medicine for Prednisolone 30mg Tablets is Prednisolon Pfizer 5 mg (Pfizer AB, Sweden).

Prednisolone Tablets belong to a group of medicines called steroids. Their full name is corticosteroids. These corticosteroids occur naturally in the body. Boosting the body with extra corticosteroids (such as Prednisolone Tablets) is an effective way to treat various illnesses involving inflammation in the body. Prednisolone Tablets are used in a wide range of inflammatory and auto-immune conditions including:

- allergies, including severe allergic reactions
- inflammation affecting the:
  - lungs, including asthma
  - blood vessels and heart
  - bowel or kidneys
  - muscles and joints, including rheumatoid arthritis
  - eye or nervous system
- skin conditions
- some infections
- some cancers, including leukaemia, lymphoma and myeloma
- to prevent organ rejection after a transplant.

Also:

- to boost steroid levels when the body is not making enough natural steroid on its own
- to treat high calcium levels.

How do Prednisolone Tablets work?
Prednisolone, the active ingredient, helps to maintain health and wellbeing. Prednisolone acts by reducing the inflammation caused by these illnesses, which could otherwise go on making such conditions worse. The patient must take this medicine regularly to get maximum benefit from it.

How are Prednisolone Tablets used?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth).

The patient will be supplied with a 'Steroid Treatment Card' which includes important details of their treatment. This card should be carried at all times.

The patient must always take this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

Different illnesses require different doses of Prednisolone Tablets. Depending on the patient's illness, their daily dose may be between 5 and 60 mg. In some cases the patient may be instructed to take it every other day.

The patient's doctor will decide when and how to treat them with Prednisolone Tablets.

Once the patient's condition starts to get better, their doctor may change their dosage to a lower one. The patient's doctor may also reduce their dosage before stopping treatment completely. This may depend on the patient's illness, the dosage and how long they have been taking this medicine. In all cases the patient should be careful to follow any changes.

Treatment of the elderly
When steroids are taken by elderly patients some of the unwanted side effects can be more serious especially brittle bone disease, diabetes, high blood pressure, infections and thinning of the skin.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

What benefits of Prednisolone Tablets have been shown in studies?
As Prednisolone Tablets are generic/hybrid generic medicines of Prednisolon Pfizer 2.5 mg, 5 mg and 10 mg (Pfizer AB, Sweden), studies have been limited to tests to determine that Prednisolone Tablets are bioequivalent/therapeutically equivalent to the reference medicines Prednisolon Pfizer 2.5 mg, 5 mg and 10 mg (Pfizer AB, Sweden). 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 Tablets?
Because Prednisolone Tablets are either generic or hybrid generic medicines that are considered bioequivalent/therapeutically equivalent to the reference medicines Prednisolon Pfizer 2.5 mg, 5 mg and 10 mg (Pfizer AB, Sweden) the benefits and possible side effects are taken as being the same as the reference medicines.

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

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

Why was Prednisolone Tablets approved?
It was concluded that, in accordance with EU requirements, Prednisolone Tablets have been shown to have comparable quality and to be bioequivalent/be comparable to Prednisolon Pfizer 2.5 mg, 5 mg and 10 mg (Pfizer AB, Sweden). Therefore, the MHRA decided that, as for Prednisolon Pfizer 2.5 mg, 5 mg and 10 mg (Pfizer AB, Sweden); the benefits are greater than the risks and recommended that Prednisolone Tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Prednisolone Tablets?
A risk management plan (RMP) has been developed to ensure that Prednisolone Tablets is used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflet for Prednisolone 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 Tablets
Malta and the UK agreed to grant marketing authorisations for Prednisolone Tablets on 21 March 2016. Marketing authorisations were granted in the UK on 01 April 2016.

The full PAR for Prednisolone Tablets follows this summary.

For more information about use of Prednisolone Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2016.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Caduceus Pharma Ltd, marketing authorisations for the medicinal products Prednisolone 2.5mg, 5mg, 10mg, 20mg, 25mg and 30mg Tablets (PL 24668/0296-301; UK/H/6012/001-006/DC). The products are prescription-only medicines (POM) indicated for:

- **Allergy and anaphylaxis**: bronchial asthma, drug hypersensitivity reactions, serum sickness, angioneurotic oedema, anaphylaxis, incapacitating allergies unresponsive to conventional treatment.
- **Arteritis/collagenosis**: giant cell arteritis/polymyalgia rheumatica, mixed connective tissue disease, polyarteritis nodosa, polymyositis.
- **Blood disorders**: haemolytic anaemia (auto-immune), leukaemia (acute and chronic lymphocytic), lymphoma, multiple myeloma, idiopathic thrombocytopenic purpura.
- **Cardiovascular disorders**: post-myocardial infarction syndrome, rheumatic fever with severe carditis.
- **Endocrine disorders**: primary and secondary adrenal insufficiency, congenital adrenal hyperplasia.
- **Gastro-intestinal disorders**: regional ileitis (Crohn's disease), ulcerative colitis, persistent coeliac syndrome (coeliac disease unresponsive to gluten withdrawal), auto-immune chronic active hepatitis, multisystem disease affecting liver, biliary peritonitis.
- **Hypercalcaemia**: sarcoidosis, vitamin D excess.
- **Infections (with appropriate chemotherapy)**: helminthic infestations, Herxheimer reaction, infectious mononucleosis, miliary tuberculosis, mumps orchitis (adult), tuberculous meningitis, rickettsial disease.
- **Muscular disorders**: polymyositis, dermatomyositis.
- **Neurological disorders**: infantile spasms, Shy-Drager syndrome, sub-acute demyelinating polyneuropathy.
- **Ocular disease**: scleritis, posterior uveitis, retinal vasculitis, pseudo-tumours of the orbit, giant cell arteritis, malignant ophthalmic Graves disease.
- **Renal disorders**: lupus nephritis, acute interstitial nephritis, minimal change glomerulonephritis, nephrotic syndrome.
- **Respiratory disease**: allergic pneumonitis, asthma, occupational asthma, pulmonary aspergillosis, pulmonary fibrosis, pulmonary alveolitis, aspiration of foreign body, aspiration of stomach contents, pulmonary sarcoid, drug induced lung disease, adult respiratory distress syndrome, spasmodic croup, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculosis chemotherapy.
- **Rheumatic disorders**: rheumatoid arthritis, polymyalgia rheumatica, juvenile chronic arthritis, psoriatic arthritis, systemic lupus erythematosus, dermatomyositis, mixed connective tissue disease.
- **Skin disorders**: pemphigus vulgaris, exfoliative dermatitis, bullous pemphigoid, systemic lupus erythematosus, pyoderma gangrenosum.
- **Miscellaneous**: sarcoidosis, hyperpyrexia, Behçets disease, immunosuppression in organ transplantation.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Malta as Concerned Member State (CMS). The applications for Prednisolone 2.5 mg, 5mg and 10mg Tablets were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The applications for Prednisolone 20mg, 25mg and 30mg Tablets (PL 24668/0299-301; UK/H/6012/004-006/DC) were submitted under Article 10(3) of Directive 2001/83/EC, as amended, as hybrid applications.

The reference medicinal products for these applications are Prednisolon Pfizer 2.5 mg, 5 mg and 10 mg authorised to Pfizer AB, Sweden, on 09 March 1984 (2.5 mg and 10 mg, MA numbers 10059 and 10060 respectively) and 31st August 1973 (5 mg, MA number 8822).

The Swedish reference product is available in tablet strengths of 2.5 mg, 5 mg and 10 mg whereas the proposed Prednisolone 20 mg, 25 mg, and 30 mg tablets represent additional tablet strengths.

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 is approximately three times more potent on a weight for weight basis than hydrocortisone with respect to glucocorticoid activity; however, it is considerably less potent than hydrocortisone in mineralocorticocoid activity which reduces the 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.

Two bioequivalence studies (conducted under fasting conditions) were submitted to support these applications. Comparing the applicant’s test products Prednisolone 2.5mg and 30mg Tablets (Caduceus Pharma Ltd) with the reference products Prednisolon Pfizer 2.5 mg and 10 mg (administered at 3 x 10 mg tablets) authorised to Pfizer AB, Sweden. The applicant has stated that the bioequivalence studies were conducted in accordance with the clinical research guidelines laid out in the Indian Council for Medical Research (ICMR) guidelines for biomedical research on human subjects, the current Helsinki Declaration (Brazil 2013), ICH guidelines on Good Clinical Practice (GCP) and applicable regulatory requirements.

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that these applications were based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

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 applications could be approved at the end of procedure on 21 March 2016. After a subsequent national phase, licences were granted in the UK on 01 April 2016.

II QUALITY ASPECTS

II.1 Introduction

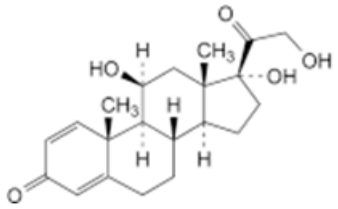
Each tablet contains 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg or 30 mg prednisolone, as the active ingredient. Other ingredients consist of the pharmaceutical excipients lactose monohydrate, pregelatinised starch, sodium starch glycolate, type A, iron oxide yellow (E172), iron oxide red (E172), glycerol dibehenate and magnesium stearate.

All strengths of the finished product are packed in to aluminium (Al)/polyvinyl chloride (PVC) blisters and are available in pack sizes of 28 tablets. The 25 mg strength tablets are also available in packs of 56 tablets. Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance

INN: Prednisolone
Chemical name: 11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione.

Structure:



Molecular formula: $C_{21}H_{28}O_5$
Molecular weight: 360.4
Description: White or almost white, crystalline, hygroscopic powder.
Solubility; Very slightly soluble in water, soluble in ethanol (96 per cent) and in methanol, sparingly soluble in acetone, slightly soluble in methylene chloride.

Prednisolone is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, prednisolone, are covered by the 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 tablets containing 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg or 30 mg prednisolone per tablet, that are generic/hybrid generic versions of the reference products Prednisolon Pfizer 2.5 mg, 5 mg and 10 mg (Pfizer AB, Sweden). A satisfactory account of the pharmaceutical development has been provided.

Comparative *in-vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of iron oxide yellow (E172), iron oxide red (E172) which are in compliance the United States Pharmacopeia and National Formulary (USP-NF). Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

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 monohydrate is sourced from healthy animals under the same conditons 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 this product.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot scale batch size and has shown satisfactory results. The marketing authorisation holder (MAH) has committed to perform additional process validation studies on future commercial-scale batches.

Finished Product Specification
The finished product specifications proposed are acceptable. 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 the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months with the storage conditions ‘Keep the blister packs in the outer carton in order to protect from light.’

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

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of these applications from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of prednisolone 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 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.

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 Prednisolone Tablets are intended for generic substitution, this 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

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic/ hybrid generic medicinal products of originator products that have been licensed for over 10 years.

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of prednisolone is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

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 prednisolone.

Based on the data provided, Prednisolone Tablets can be considered bioequivalent/be comparable to Prednisolon Pfizer 2.5 mg, 5 mg and 10 mg (Pfizer AB, Sweden)

IV.2 Pharmacokinetics

Two bioequivalence studies representing extremes of the proposed range of tablet strengths (2.5 mg and 30 mg) have been supplied in support of bioequivalence for all the proposed tablet strengths. A bracketed approach has been used due to the existence of non-proportional composition (between active substance and core excipients) across the tablet strengths. Furthermore, prednisolone is well recognised to display non-linear pharmacokinetics thought to be due principally to non-linear plasma protein binding, resulting in higher clearance rates with increasing dose. Prednisolone concentrations in plasma after single oral doses of 20 mg and 40 mg are reported to be very similar. Increasing dose would

therefore be predicted to result in a less than proportional increase in plasma concentrations with increasing dose.

The bracketed approach – where the highest and lowest tablet strengths are studied – is an acceptable approach for the investigation of bioequivalence where non-linear pharmacokinetics are associated with a less than proportional increase in AUC and C_{max} over the range of tablet strengths. The Applicant has also supplied dissolution data that reveal a similarity f_2 factor higher than 50 over the range of physiologically relevant pH for the higher tablet strengths.

The supply of two bioequivalence studies at the extremes of the range of proposed tablet strengths is therefore acceptable to infer bioequivalence across all tablet strengths.

In support of these applications, the applicant submitted the following bioequivalence studies:

STUDY 1
A randomised, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of the applicant's test product Prednisolone 2.5mg Tablets (Caduceus Pharma Ltd) versus the reference product Prednisolon Pfizer 2.5 mg tablets (Pfizer AB, Sweden) in healthy, adult, subjects under fasting conditions.

Following an overnight fast, subjects were administered a single dose (1 x 2.5 mg tablet) of the test or the reference product with 240 mL of water.

Blood samples were collected for plasma levels before dosing and up to and including 24 hours after each administration. The washout period between the treatment phases was 3 days. The pharmacokinetic results are presented below:

Table: Summary of pharmacokinetic parameters for prednisolone:

Pharmacokinetic parameter	Geometric mean	Arithmetic mean	Standard deviation
Reference Product			
AUC_{0-t} (ng.h/mL)	463.79	474.69	99.289
C_{max} (ng/mL)	107.02	108.98	19.592
Test product			
AUC_{0-t} (ng.h/mL)	459.20	469.84	101.084
C_{max} (ng/mL)	107.72	110.22	24.177

AUC_{0-t} area under the plasma concentration-time curve from zero to t hours
AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration

Table: 90% confidence intervals calculated using ln-transformed data:

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio (%)	98.92	99.03	100.50
90% geometric C.I.	96.77 - 101.13	96.91 - 101.18	95.61 - 105.64
Intra-subject CV (%)	4.73	4.63	10.76

STUDY 2
A randomised, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of the applicant's test product Prednisolone 30mg Tablets (Caduceus Pharma Ltd) versus the reference product 3 x Prednisolon Pfizer 10 mg tablets (Pfizer AB, Sweden) in healthy, adult, subjects under fasting conditions.

Following an overnight fast, subjects were administered a single dose of the test (1 x 30 mg tablet) or the reference product (3 x 10 mg tablets) with 240 mL of water.

Blood samples were collected for plasma levels before dosing and up to and including 24 hours after each administration. The washout period between the treatment phases was 3 days. The pharmacokinetic results are presented below:

Table: Summary of pharmacokinetic parameters for prednisolone:

Pharmacokinetic parameter	Geometric mean	Arithmetic mean	Standard deviation
Reference Product			
AUC_{0-t} (ng.h/mL)	2272.84	2308.94	402.421
C_{max} (ng/mL)	463.01	471.47	92.978
Test product			
AUC_{0-t} (ng.h/mL)	2285.87	2322.35	408.240
C_{max} (ng/mL)	433.10	442.16	90.228

AUC_{0-t} area under the plasma concentration-time curve from zero to t hours
AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration

Table: Ratio and 90% Confidence Intervals of test product versus Reference Product:

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio (%)	100.57	100.61	93.54
90% geometric C.I.	99.30 - 101.86	99.41 - 101.83	89.74 - 97.50
Intra-subject CV (%)	3.38	3.18	11.03

Conclusion
The 90% confidence intervals of the test/reference ratio for AUC and C_{max} values for prednisolone for the 2.5 mg and 30 mg test product strengths 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**). Thus, the data support the claim that the applicant's test products Prednisolone 2.5mg and 30mg Tablets (Caduceus Pharma Ltd) are bioequivalent to the reference products Prednisolon Pfizer 2.5 mg and 10 mg (administered at 3 x 10 mg tablets) [Pfizer AB, Sweden].

As the 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg or 30 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence studies with the 2.5 mg and 30 mg tablet strengths can be extrapolated to the 5 mg, 10 mg, 20 mg and 25 mg strength tablets.

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 are required.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

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 Prednisolone Tablets.

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

Summary of safety concerns	
Important identified risks	• Immunosuppression leading to increased susceptibility to infection and a greater risk of atypical and severe presentation of infection, including bacterial, viral (e.g. chicken pox and measles), fungal and protozoal infections; particularly infection with opportunistic and/or intracellular pathogens and tuberculosis • Abrupt withdrawal of prednisolone leading to disease relapse • Abrupt withdrawal of prednisolone leading to adrenocortical insufficiency • Live virus immunisation • Hypersensitivity reactions • Risk of ocular herpes simplex because of possible perforation • Sodium and water retention (leading to worsening of hypertension and cardiac failure, and complicating management of renal failure) • Increased risk for, or deterioration of, diabetes mellitus • Increased risk for, or deterioration of, osteoporosis • Increased risk for, or deterioration of, glaucoma and/or cataract • Deterioration of epilepsy • Increased risk for, or deterioration of, severe affective disorders including frank psychosis, suicidal ideation and suicide • Increased risk for, or deterioration of, peptic ulceration • Steroid myopathy • Dose-related growth retardation in infants, children and adolescents, which may be irreversible • Increased risk for, or deterioration of, hypokalaemia • Increased risk for thinning of skin
Important potential risks	• Malignancy due to chronic immunosuppression (e.g. Kaposi's sarcoma)
Missing information	• Not applicable

Summary table of risk minimisation measures:

Important identified risks		
Safety concern	**Summary of Routine Risk Minimisation Activities**	**Summary of Additional Risk Minimisation Activities**
Immunosuppression leading to increased susceptibility to infection and a greater risk of atypical and severe presentation of infection, including bacterial, viral (e.g. chicken pox and measles), fungal and protozoal infections; particularly infection with opportunistic and/or intracellular pathogens and tuberculosis	Routine risk minimisation measures are sufficient for this safety concern as information is included in sections 4.3, 4.4 and 4.8 of the SmPC.	N/A
Abrupt withdrawal of prednisolone leading to disease relapse	Routine risk minimisation measures are sufficient for this safety concern as information is included in sections 4.2, 4.4 and 4.8 of the SmPC.	N/A
Abrupt withdrawal of prednisolone leading to adrenocortical insufficiency	Routine risk minimisation measures are sufficient for this safety concern as information is included in sections 4.4 and 4.8 of the SmPC.	N/A
Live virus immunisation	Routine risk minimisation measures are sufficient for this safety concern as information is included in sections 4.4 and 4.5 of the SmPC	N/A
Hypersensitivity reactions	Routine risk minimisation measures are sufficient for this safety concern as information is included in sections 4.3 and 4.8 of the SmPC.	N/A
Risk of ocular herpes simplex because of possible perforation	Routine risk minimisation measures are sufficient for this safety concern as information is included in sections 4.3 and 4.4 of the SmPC.	N/A
Sodium and water retention (leading to worsening of hypertension and cardiac failure, and complicating management of renal failure)	Routine risk minimisation measures are sufficient for this safety concern as information is included in section 4.8 of the SmPC.	N/A
Increased risk for, or deterioration of, diabetes mellitus	Routine risk minimisation measures are sufficient for this safety concern as information is included in section 4.4, 4.5 and 4.8 of the SmPC.	N/A
Increased risk for, or	Routine risk minimisation	N/A

deterioration of, osteoporosis	measures are sufficient for this safety concern as information is included in section 4.4 and 4.8 of the SmPC.	
Increased risk for, or deterioration of, glaucoma and/or cataract	Routine risk minimisation measures are sufficient for this safety concern as information is included in section 4.4 and 4.8 of the SmPC.	N/A
Deterioration of epilepsy	Routine risk minimisation measures are sufficient for this safety concern as information is included in section 4.8 of the SmPC.	N/A
Increased risk for, or deterioration of, severe affective disorders including frank psychosis, suicidal ideation and suicide	Routine risk minimisation measures are sufficient for this safety concern as information is included in sections 4.4 and 4.8 of the SmPC.	N/A
Increased risk for, or deterioration of, peptic ulceration	Routine risk minimisation measures are sufficient for this safety concern as information is included in section 4.4 and 4.8 of the SmPC.	N/A
Steroid myopathy	Routine risk minimisation measures are sufficient for this safety concern as information is included in sections 4.4 and 4.8 of the SmPC.	N/A
Dose-related growth retardation in infants, children and adolescents, which may be irreversible	Routine risk minimisation measures are sufficient for this safety concern as information is included in sections 4.4 and 4.8 of the SmPC.	N/A
Increased risk for, or deterioration of, hypokalaemia	Routine risk minimisation measures are sufficient for this safety concern as information is included in section 4.4, 4.5 and 4.8 of the SmPC:	N/A
Increased risk for thinning of skin	Routine risk minimisation measures are sufficient for this safety concern as information is included in sections 4.4 and 4.8 of the SmPC.	N/A

Important potential risks		
Safety concern	**Summary of Routine Risk Minimisation Activities**	**Summary of Additional Risk Minimisation Activities**
Malignancy due to chronic immunosuppression (e.g. Kaposi's sarcoma)	Routine risk minimisation measures are sufficient for this safety concern as information is included in section 4.4 and 4.5 of the SmPC.	N/A

IV.7 Discussion on the clinical aspects

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the applications were based on being generic/hybrid generic medicinal products of originator products that have been licensed for over 10 years.

Bioequivalence has been demonstrated between the applicant's test products Prednisolone 2.5mg and 30mg Tablets (Caduceus Pharma Ltd) and the reference products Prednisolon Pfizer 2.5 mg and 10 mg (administered at 3 x 10 mg tablets) [Pfizer AB, Sweden].

As the 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg or 30 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence

studies with the 2.5 mg and 30 mg tablet strengths can be extrapolated to the 5 mg, 10 mg, 20 mg and 25 mg strength tablets.

The grant of marketing authorisations is recommended for these applications.

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 package leaflet was English.

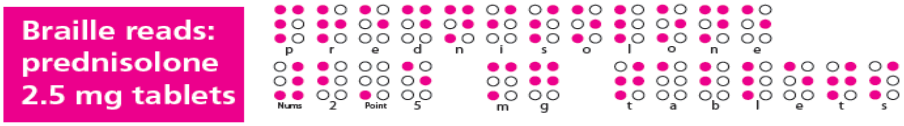
The results show that the package leaflet meets the criteria for readability, as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

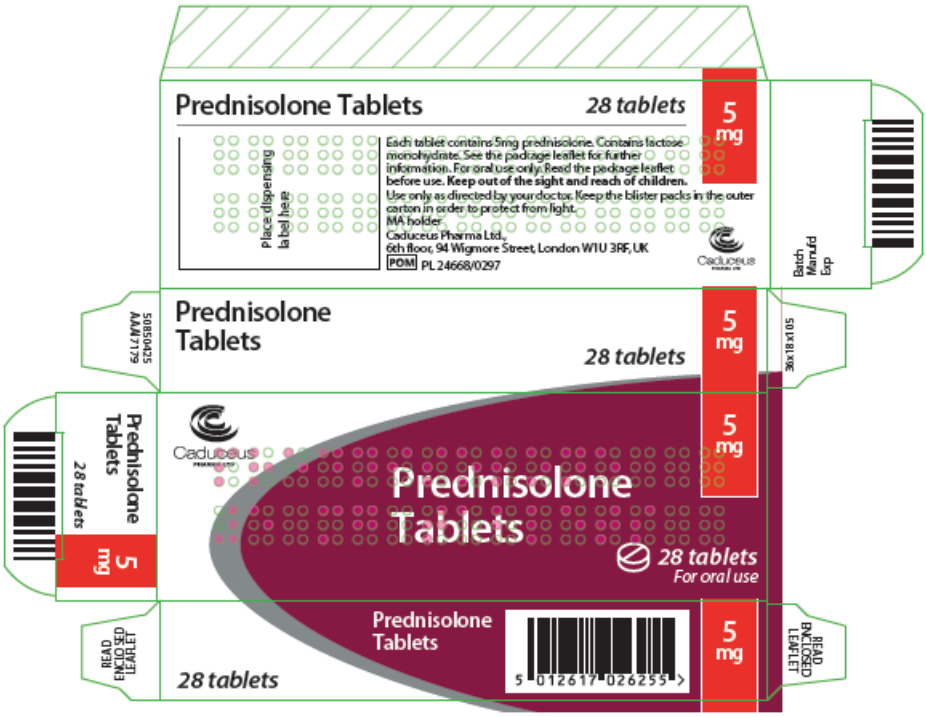
VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with prednisolone is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

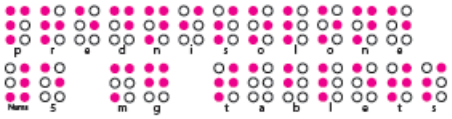
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

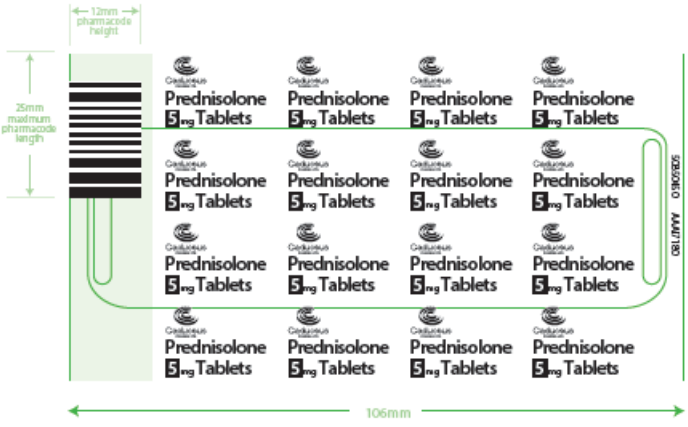
The approved labelling for this medicine is presented below:

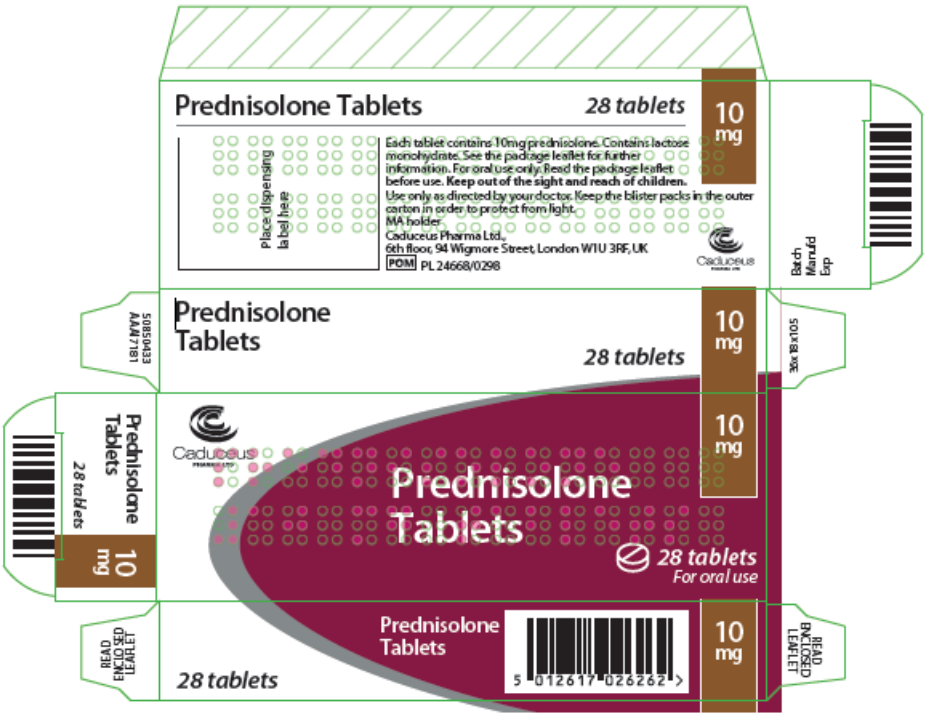




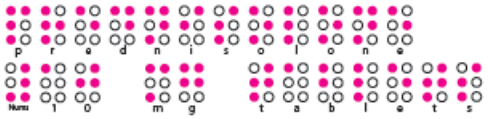
Braille reads:
prednisolone
5 mg tablets

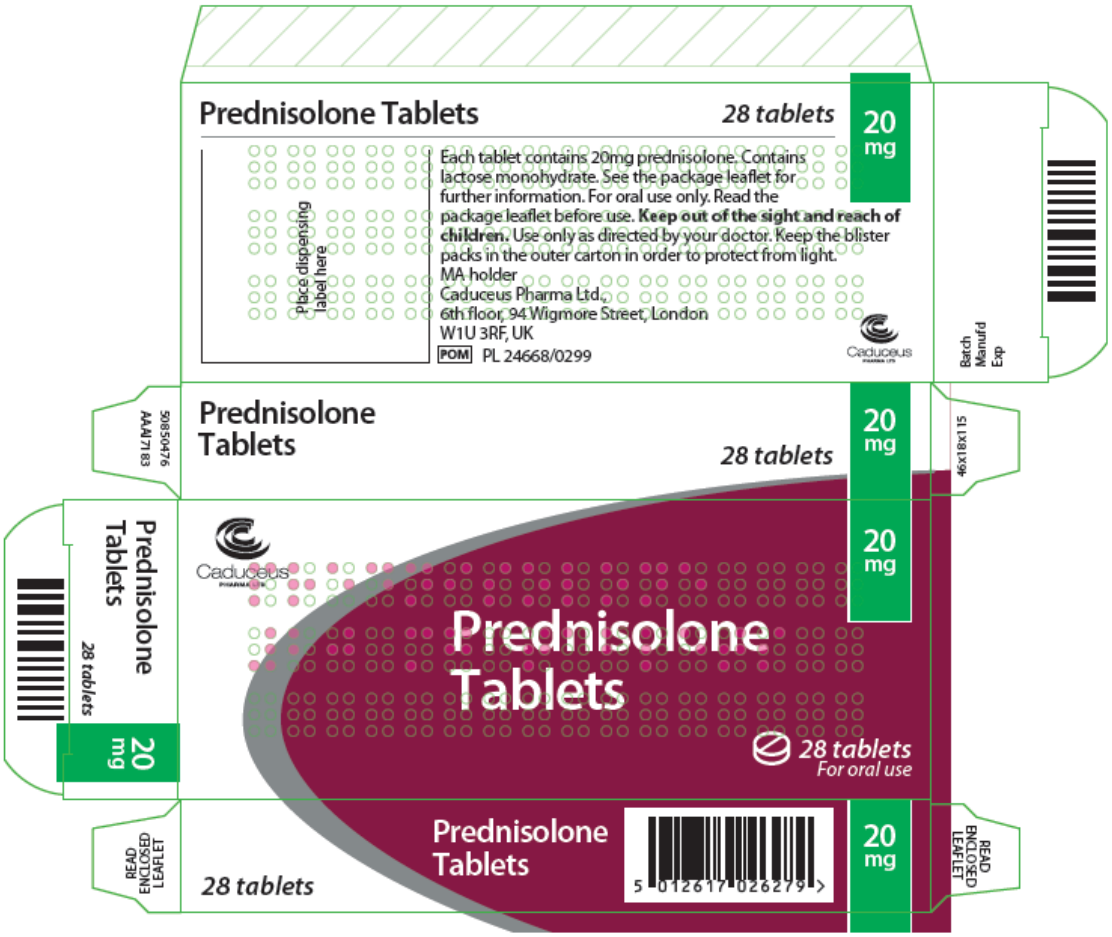




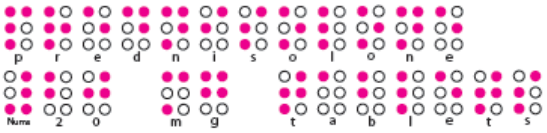


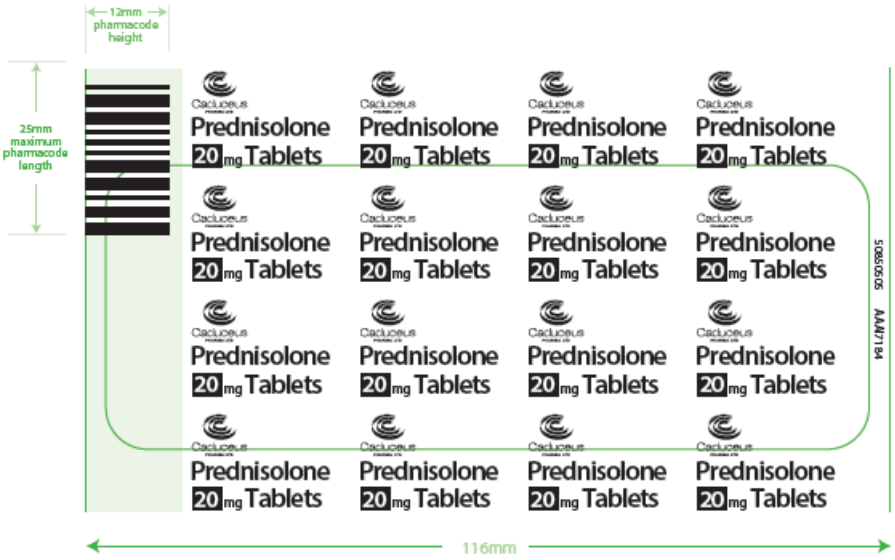
Braille reads: prednisolone 10 mg tablets

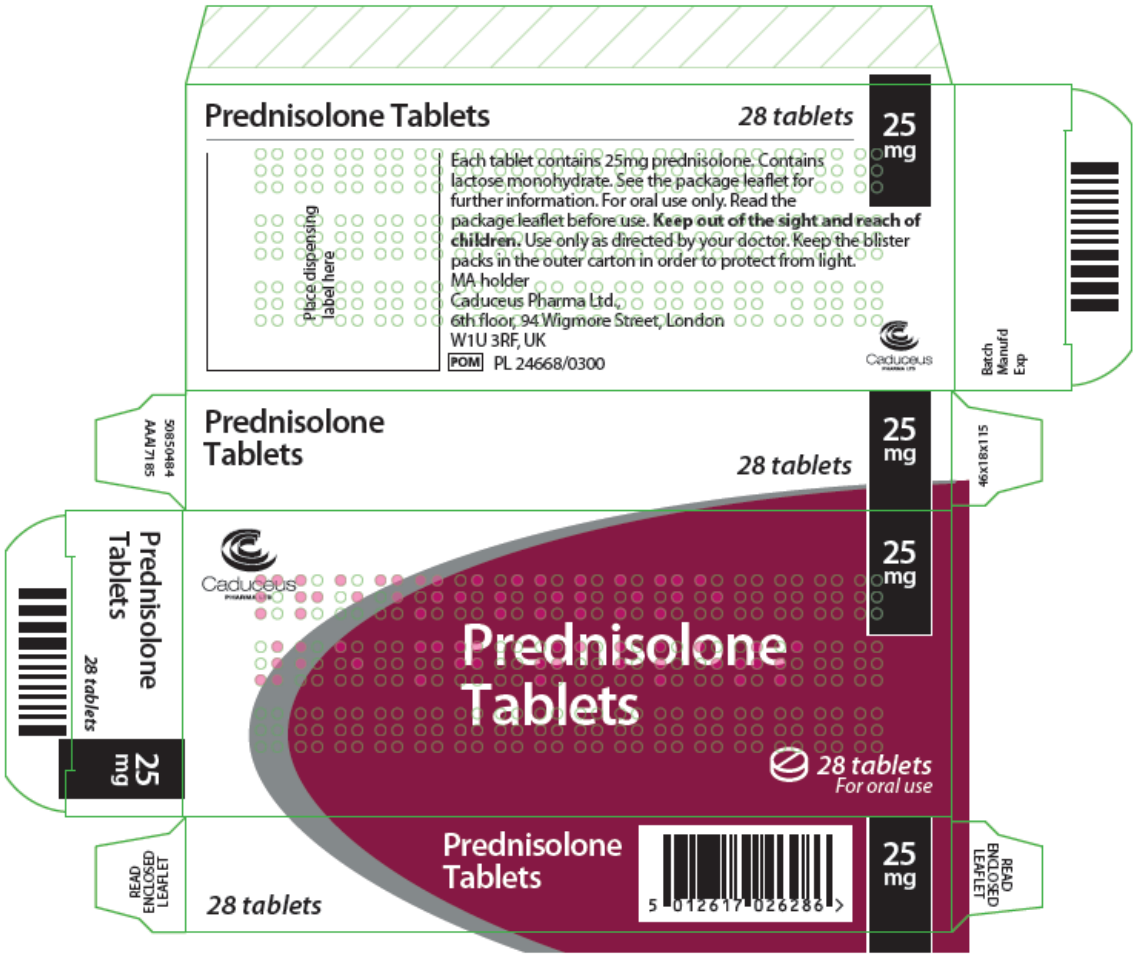


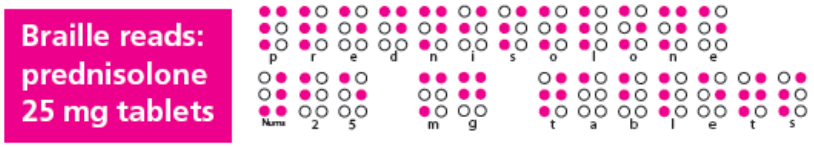


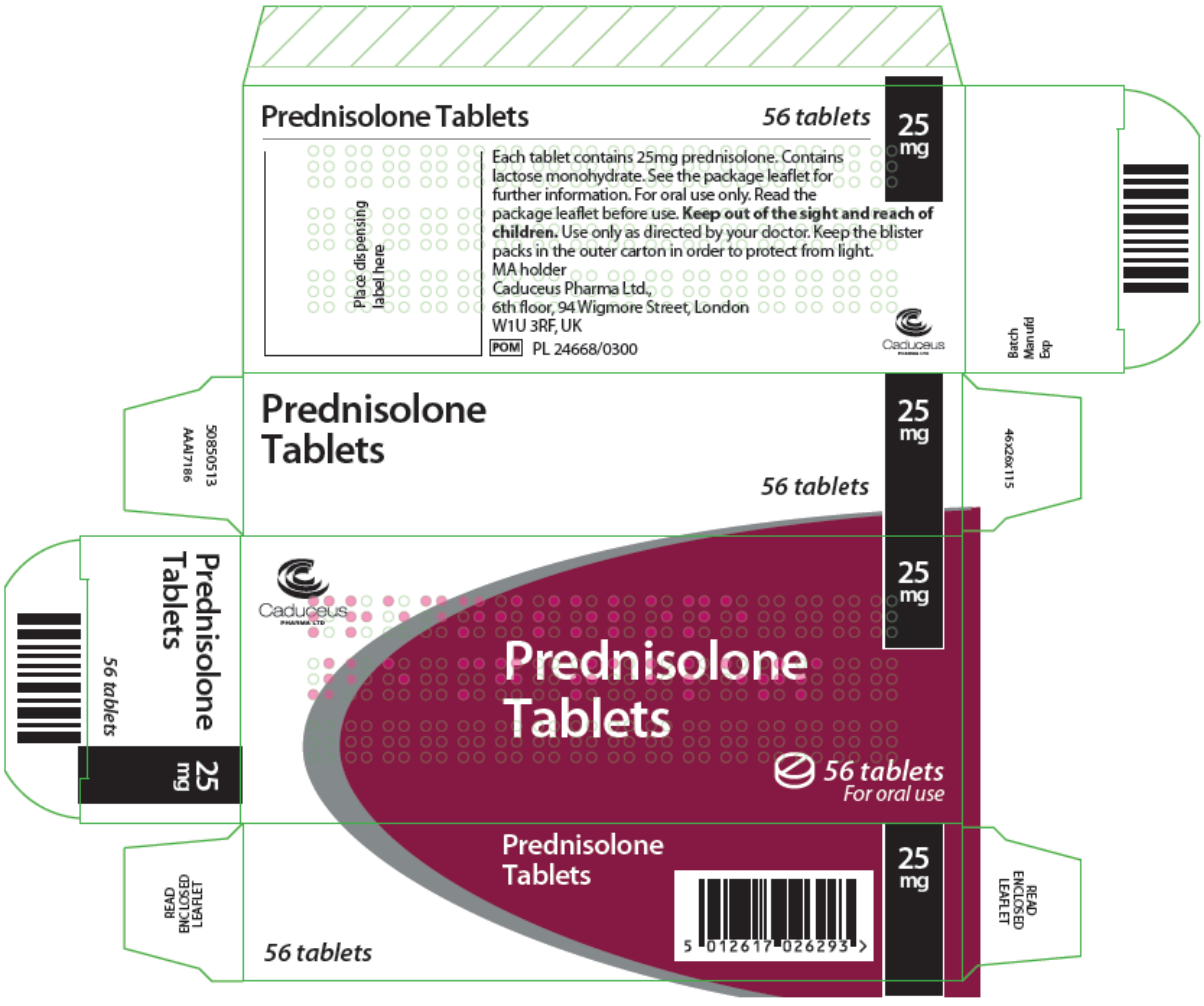
Braille reads: prednisolone 20 mg tablets



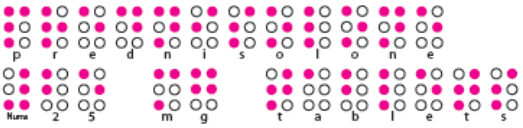


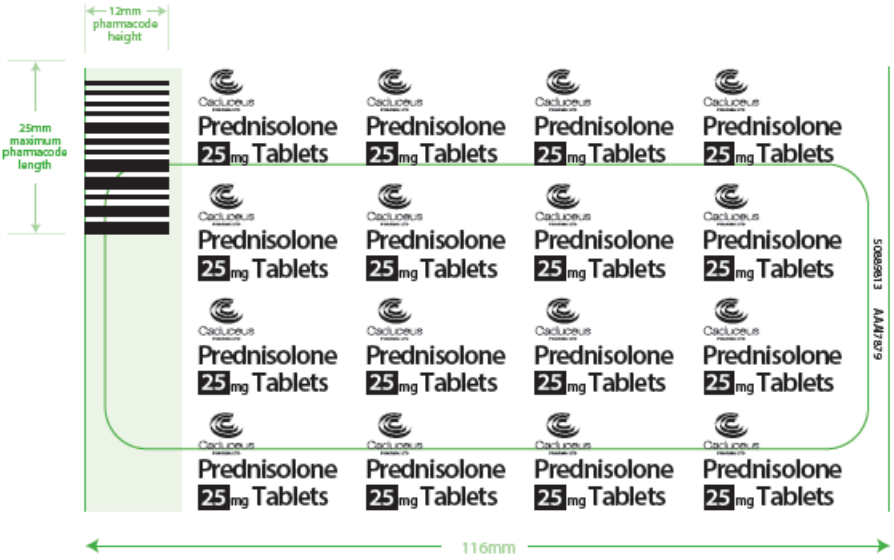

Prednisolone Tablets
28 tablets
25 mg
Each tablet contains 25mg prednisolone. Contains lactose monohydrate. See the package leaflet for further information. For oral use only. Read the package leaflet before use. Keep out of the sight and reach of children. Use only as directed by your doctor. Keep the blister packs in the outer carton in order to protect from light.
MA holder
Caduceus Pharma Ltd.,
6th floor, 94 Wigmore Street, London
W1U 3RF, UK
POM PL 24668/0300
Place dispensing label here
Batch
Manufd
Exp
50850484
AAA7165
46x118x115
Caduceus
Prednisolone Tablets
28 tablets
For oral use
READ ENCLOSED LEAFLET
5 012617 026286

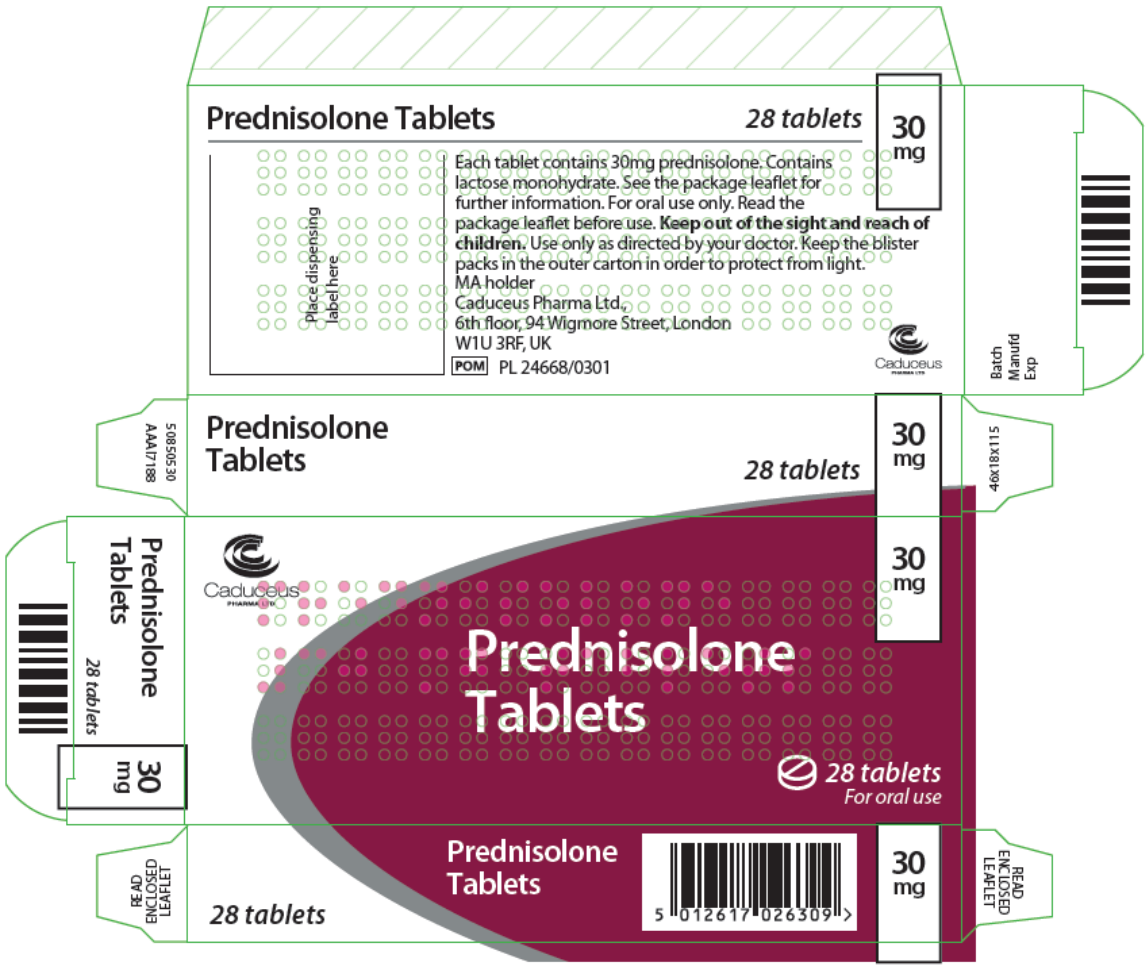

Braille reads:
prednisolone
25 mg tablets



Braille reads: prednisolone 25 mg tablets







Braille reads:
prednisolone
30 mg tablets