IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific discussion

Prednesol 5mg Tablets

PREDNISOLONE SODIUM PHOSPHATE

PA1113/001/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA granted a marketing authorisation for Prednesol 5mg Tablets from Phoenix Labs on 27th October 1978.

The following are the therapeutic indications for Prednesol 5mg Tablets:

A wide variety of diseases may sometimes require corticosteroid therapy.

Prednisolone is used principally for its anti-inflammatory and immunosuppressant action or anti-neoplastic properties. Prednisolone may also be used as a replacement therapy but cortisone is usually preferred.

The major indications are listed below. This list of indications is not exhaustive but represents the major established disease states with evidence of an established and current role in their management. Prednisolone may be used in a wide variety of other inflammatory and immune disorders according to local guidelines and according to the assessment of the benefit risk in individual patients.

Inflammatory and immunological disorders
- *Pemphigus*
- *Asthma*
- *Sarcoid disease*
- *Rheumatoid arthritis, polymyalgia rheumatica and giant cell (temporal) arteritis and polyarteritis nodosa*
- *Systemic lupus erythematosus,*
- *Polymyositis*
- *Inflammatory bowel disease: ulcerative colitis and Crohn's disease*
- *Renal disease: minimal change nephrotic syndrome, acute interstitial nephritis; renal lupus*
- *Autoimmune hepatitis,*
- *Thrombocytopenic purpura and acquired haemolytic anaemia*
- *Immunosuppression – in organ transplantation*

Neoplasms Treated with Corticosteroids
Prednisolone is an established component of chemotherapeutic regimes used in the treatment of the following neoplasms:
- *Acute Lymphoblastic Leukemia (including the acute blastic phase of myeloid leukaemia resembling acute lymphoblastic leukemia)*
- *Chronic Lymphocytic Leukemia*
- *Hodgkin Lymphoma*
- *Non-Hodgkin Lymphoma*

Prednisolone is a synthetic steroid - 11b, 17a, 21-trihydroxypregna-1, 4-diene-3, 20- dione. Prednisolone was introduced into clinical use in 1955 and is now widely available from many manufacturers in a variety of formulations, and used for a significant number of inflammatory and neoplastic conditions.

This prednisolone product was developed as a rapid dissolution oral preparation.

The Applicant, Phoenix Labs, has upgraded the original dossier for Prednesol 5mg Tablets for the purpose of making this Mutual Recognition Procedure (MRP) application with Ireland as Reference Member State. No new *in-vivo* data are generated. Also, no bioequivalence studies were necessary on the basis that this is the innovator product. Instead the clinical part of this dossier was updated following a comprehensive bibliographic review of prednisolone which is a well-established drug substance. The quality and preclinical parts of the dossier were also updated.

Prednesol 5 mg tablets were originally approved in Ireland following a full national application, and hence the legal basis for this Mutual Recognition Procedure (MRP) is Article 8(3) of Directive 2001/83/EC. IE acted as reference member state (RMS), with the UK as the only concerned member state (CMS). Of note the name for this medicinal

product in the UK will be Prednisolone 5mg Soluble Tablets.

The legal supply status in Ireland for this product is available on prescription only, which cannot be renewed.

The Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA's website.

Name of the product	Prednesol 5mg Tablets
Name(s) of the active substance(s) (INN)	PREDNISOLONE SODIUM PHOSPHATE
Pharmacotherapeutic classification (ATC code)	H02AB06 Glucocorticoids
Pharmaceutical form and strength(s)	5 milligram
Marketing Authorisation Number(s) in Ireland (PA)	PA1113/001/001
Marketing Authorisation Holder	Phoenix Labs
MRP/DCP No.	IE/H/472/001/MR
Reference Member State	IE
Concerned Member State	UK

II QUALITY ASPECTS

II.1. Introduction

This application is for Prednesol 5mg Tablets.

II.2 Drug substance

The active substance is prednisolone sodium phosphate, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Prednesol 5mg Tablets contain 5 mg of prednisolone.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Prednesol 5mg Tablets.

III NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of prednisolone are well-known and no new non-clinical data has been submitted which is appropriate.

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

IV CLINICAL ASPECTS

IV.1 Introduction

Prednisolone is a well-known active substance with established efficacy and tolerability. On the basis that the original submission dossier for Prednesol 5mg tablets dates back to the 1970s, the applicant has reviewed and updated the clinical dossier based on a comprehensive bibliographic review, to ensure that the dossier is up to date and is reflective of the use of oral prednisolone in current clinical practice.

IV.2 Pharmacokinetics

The pharmacokinetics of prednisolone after oral administration in humans has been well characterised and has evolved from the time of first development in the 1960s, with further studies carried out in the 1980s and 1990s.

Absorption

Prednisolone is readily absorbed from the gastrointestinal tract with peak plasma concentrations achieved by 1-2 hours after an oral dose. Plasma prednisolone extensively bound to plasma proteins (70%-90%), with binding to albumin and

corticosteroid-binding globulin. The plasma half-life of prednisolone, after a single dose, is between 2.5-3.5 hours.

Distribution
The volume of distribution and clearance of total and unbound prednisolone are concentration dependent, and this has been attributed to saturable protein binding over the therapeutic plasma concentration range.

Elimination/Excretion
Over 90% of the prednisolone dose is excreted in the urine, with 7-30% as free prednisolone, and the remainder being recovered as a variety of metabolites.

Metabolism
Prednisolone is extensively metabolised, mainly in the liver, but the metabolic pathways are not clearly defined.

In relation to both hepatic and renal impairment, there are insufficient data to provide specific dosing advice. However reduced dosing is advised in both cases as prednisolone is known to undergo hepatic metabolism and renal excretion.

Similarly, in relation to the effect of age on the pharmacokinetics of prednisolone, the data are limited. While the small amount of data available do not identify age having an effect on the pharmacokinetic profile, exposure may be increased due to other factors such as renal or hepatic impairment which occur more frequently with age.

There are very little data available on pharmacokinetic drug- drug interactions with prednisolone. There are a number of drug interactions listed in Section 4.5 of the SmPC: these are based on literature reports, case reports, reports of interactions arising from the interacting drug's SmPC, and mostly are pharmacodynamic drug interactions.

IV.3 Pharmacodynamics

The pharmacodynamic actions of prednisolone are common to corticosteroids and naturally occurring cortisol. The actions affect virtually all cells in the body and are complex and profound.

Prednisolone acts by binding to glucocorticoid receptors found in many different types of tissue. The steroid/receptor complexes interact with cellular DNA in the nucleus, binding to steroid-response elements and modifying gene transcription. They both induce synthesis of some genes and, therefore, some proteins, and inhibit synthesis of other genes. Not all metabolic actions on genes are known. The pharmacodynamic actions of prednisolone give rise to the clinical effects of suppression of inflammation and immune response and also to adverse effects such as changes in glucose homeostasis, proteolysis and lipolysis.
Glucocorticoids also induce apoptosis (or programmed cell death) in certain lymphoid cell populations, which gives rise to its use in certain cancers.

IV.4 Clinical Efficacy

Prednisolone is long established in treating a wide range of clinical conditions. Its uses and indications result from its anti-inflammatory, immunosuppressive and anti-neoplastic effects.

Support for the use of prednisolone in the conditions outlined comes from years of clinical practice, medical literature and respected clinical guidelines. In most cases clinical practice has evolved so that there are tailored prednisolone doses and regimes specific to the indications, and for this reason it is appropriate that the product information makes clear that the doses recommended are provided as general guidance only, and that disease specific guidance should be consulted for dosing advice.

The applicant provides supporting evidence from a detailed review of the literature and guidelines to support each of the listed indications.

Although there was not a structured clinical development programme as there now is for new medicines, there is a wealth of cumulative knowledge and experience from 60 years of prescribing prednisolone.

IV.5 Clinical Safety

The safety profile of prednisolone is well known given the long number of years in use, and is shared with other oral corticosteroids. The world-wide marketing experience with prednisolone is among the most extensive for any drug.

Most of the adverse events are in keeping with the known glucocorticoid and mineralocorticoid pharmacological action of steroid. While prednisolone can potentially cause a number of serious adverse effects such as adrenal suppression and withdrawal symptoms, immune function suppression, psychiatric effects, growth retardation in children, endocrine and metabolic changes(skin thinning, hirsutism, fluid retention, weight gain, impaired glucose tolerance, osteoporosis), there is good awareness around these adverse effects, and the advice to use the lowest possible dose for the shortest possible duration is well established, and well represented in the product information, and in the Risk Management Plan (RMP).

Pharmacovigilance System
The marketing authorisation holder (MAH) submitted a summary of the Pharmacovigilance System, including confirmation of the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

Risk Management Plan
The applicant has provided an RMP (version 01)

The proposed summary of safety concerns are as follows:

Important identified risks:

1. Adrenal cortical atrophy
2. Suppression of inflammatory responses and immune function: increased susceptibility to infections including risk of chicken pox or tuberculosis, and risks associated with use of live vaccines.
3. Psychiatric reactions, sometimes severe, particularly in patients with a history of affective disorders.
4. Endocrine and metabolic changes

   (i) Cushingoid facies, hirsutism and weight
   (ii) Decreased carbohydrate tolerance, particular in diabetic patients.
5. Osteoporosis
6. Growth retardation in children.
7. Withdrawal symptoms, particularly after treatment for more than 3 weeks.
8. Peptic ulceration, perforation and haemorrhage.
9. Increased risk of adverse events in patients with renal or liver insufficiency
10. Increased intra-ocular pressure, including glaucoma.

Important potential risk

1. Use in pregnancy and lactation

Missing information

1. None

There is no request for additional studies.
Routine risk minimisation measures are considered sufficient. It is noted that a reduced RMP has been provided, which can be considered acceptable in view of the “well established use” type product involved. Going forward as new information becomes available on use of the product, the applicant is reminded to ensure the RMP is updated as per GVP requirements.

With regard to PSUR submission, the applicant should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the applicant should follow the DLP according to the EURD list

IV.6 Discussion on the clinical aspects

The body of evidence from the literature together with experience of the established use of prednisolone provide reassurance for its effective use for the given indications. Prednesol 5mg tablets have been marketed in Ireland since 1978. Their efficacy and safety are well established.

V OVERALL CONCLUSIONS

Prednisolone is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The applicant has submitted data, and an updated dossier to confirm the benefit and demonstrate an acceptable safety profile for Prednesol 5mg tablets. The HPRA consider that the benefit risk of Prednesol 5mg tablets in the proposed indications is positive.

In this MRP application, the CMS (UK) has endorsed the assessment of the RMS, and the procedure has concluded positively.

Following MRP/DCP procedure:
The marketing authorisation holder will submit a variation through the mutual recognition procedure after the approval of the marketing authorisation in the CMS (UK) to make some agreed minor changes to the patient information leaflet.