LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Prednisolon G.L. Pharma
(prednisolone)

SE/H/2604/01/DC

This module reflects the scientific discussion for the approval of Prednisolon G.L. Pharma. The procedure was finalised at 2025-10-21. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Prednisolon G.L. Pharma, 5 mg, Tablet.

The active substance is prednisolone. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Prednisolone is a synthetic glucocorticoid (GC). Glucocorticoids are a class of endogenous or synthetic steroid hormones that exhibit potent anti-inflammatory effects by regulating expression of inflammation-related genes. The GCs also influence metabolism, homeostasis, development and cognition. The natural endogenous GC is cortisol (=hydrocortisone) that produced by the adrenal gland and released into the systemic circulation.

The effects of glucocorticoids are mediated by genomic and possibly nongenomic mechanisms. Genomic mechanisms include activation of the cytosolic glucocorticoid receptor that leads to activation or repression of protein synthesis, including cytokines, chemokines, inflammatory enzymes and adhesion molecules. Thus, inflammation and immune response mechanisms may be modified. Nongenomic mechanisms might play an additional role in glucocorticoid pulse therapy.

The claimed indication for Prednisolon G.L. Pharma is:

- Unspecified therapy in conditions where the anti-inflammatory and immunosuppressive effects of prednisolone are desired. Examples include rheumatoid arthritis, SLE, certain kinds of vasculitis, such as temporal arteritis and periarteritis nodosa, sarcoidosis, bronchial asthma, ulcerative colitis, hemolytic anemia and granulocytopenia, as well as serious allergic conditions.

- Treatment of tumours, in certain cases of acute leukaemia, lymphoma, breast cancer and prostate cancer.

Prednisolone is used over a wide dose range. The dosage must be individualized and is highly variable depending on the nature and severity of the disease, and on patient response.

Generally, the dose is 10-30 mg daily. In serious, acute cases, up to 50–60 mg or more can be given for several days. When a satisfactory effect has been reached, the daily dose should be reduced by 2.5–5 mg every second to every fifth day (more rapidly for the highest doses) to the lowest possible maintenance dose. It is desirable that this does not exceed 10 mg/24 hours.

There is no absolute maximum dosage, however, intensity and frequency of adverse events is observed to rise with increasing dose.

The therapy should be discontinued gradually, especially after high doses since the patient’s ACTH secretion may be reduced after long-term treatment.

Prednisolone is not considered to be a narrow therapeutic index drug and there is generally no need to monitor blood levels.

II.2 General comments on the submitted dossier

The application for Prednisolon G.L. Pharma, 5 mg, Tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Prednisolon Pfizer, 5 mg, tablet authorised in SE since 1973, with Pfizer AB as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS DK: Prednisolon Pfizer, 5 mg, tablet authorised in SE since 1973, with Pfizer AB as marketing authorisation holder.

The justification to use this product is based on RMS's own files. The ERP information was circulated during the validation period.

Potential similarity with orphan medicinal products
N/A

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly 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.

GMP active substance
Regarding the statement on GMP for the active substance a declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

Drug Product
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of prednisolone are well known. As prednisolone is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Prednisolon G.L. Pharma is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Clinical aspects

Pharmacokinetics

BCS-based biowaiver
The application is based on a BCS (Biopharmaceutical Classification System) based biowaiver and no bioequivalence study has been submitted. The applicant claims that prednisolone satisfy the criteria for BCS class I.

According to the ICH M9 guideline on biopharmaceutics classification system-based biowaivers (EMA/CHMP/ICH/493213/2018), a BCS class I-based biowaiver is applicable for an immediate release product if the drug substance is not considered to have a narrow therapeutic index and has been proven to exhibit high solubility and high permeability (BCS class I). Also, *in vitro* dissolution characteristics of the test and the reference product should be either very rapid or similarly rapid and the excipients that might affect bioavailability should be qualitatively the same and quantitatively similar.

Discussion and overall conclusion
The applicant has submitted literature references to support the claim that the absorption of prednisolone is complete. The applicant has referred to two studies with the absolute bioavailability of orally administered prednisolone within the range of 78 to 92%. The study by Ferry *et al*, in which the

absolute bioavailability was determined to 92%, was a well-designed study using a specific bioanalytical method and is considered to be a strong support of complete absorption. The study by Bergrem *et al*, may suggest a somewhat lower bioavailability at higher doses; 78% after 20 mg compared to 85% after 10 mg. There is also a study by Täuber *et al*., 1984, investigating the absolute bioavailability of orally administered prednisolone. This study indicated a slightly higher bioavailability for a 20 mg dose (F=89%) compared to a 10 mg dose (F=78%). The differences between doses in these studies are likely a result of normal variability. Taken together, the data are not entirely conclusive, but the overall data do indicate that the absorption of prednisolone is complete, i.e. ≥85%, which is the guideline requirement for classification as BCS class I.

The excipients are not identical in the test and reference product, but none of the excipients are known to affect drug bioavailability.

Prednisolone is not considered to be a narrow therapeutic index drug.

For quality aspects of biowaiver (solubility and dissolution), see the quality part.

In conclusion, the justification for a BCS-based biowaiver can be accepted.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system
Proposed MAH: G.L. Pharma GmbH

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan
The MAH has submitted a risk management plan, 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 Prednisolon G.L. Pharma.

Part II Safety specification

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.1 signed 9th July 2024 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH 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.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Prednisolon G.L. Pharma is found adequate. There are no objections to approval of Prednisolon G.L. Pharma, from a non-clinical and clinical point of view. The

absence of bioequivalence studies is acceptable. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments
N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**

  N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**

  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**

  N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

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 PL 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. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-