CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202020Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

A Proposed Risk Evaluation and Mitigation Strategy (REMS) for Delayed-Release Prednisone Review

Date:	June 6, 2012; *Revised June 14, 2012*
Reviewer:	Carolyn L. Yancey, M.D., F.A.A.P., Senior Medical Officer, Division of Risk Management, DRISK
Team Leader:	Kendra Worthy, Pharm. D., DRISK
Division Director	Claudia Manzo, Pharm. D., DRISK
Drug Name(s):	RAYOS [NP01 (prednisone) delayed release]
Therapeutic Class:	Glucocorticoid
Dosage and Route:	Oral Tablet: 1, 2, and 5 mg
Application/Number:	NDA 202020/ Supplement 00/Sequence 00
Subject:	A Proposed Risk Evaluation and Mitigation Strategy for Delayed-Release Prednisone (submitted on September 26, 2011/Supplement 00/Sequence 00)
Applicant:	Horizon Pharma, Inc. (previously Nitec Pharma)
OSE RCM #:	2011-4331
TSI #:	Not Applicable

CONTENTS

EXECUTIVE SUMMARY

This Division of Risk Management (DRISK), review evaluates a proposed Risk Evaluation and Mitigation Strategy (REMS) for delayed-release (DR) prednisone for the treatment of rheumatoid arthritis (RA) in adults.[1] The proposed DR prednisone tablet will be administered once daily (b) (4)
The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requests a consult from the DRISK for review of the proposed REMS submitted in this 505(b)(2) New Drug Application (NDA) 202020 on September 26, 2011.

The applicant voluntarily submitted a proposed REMS for DR prednisone including (b) (4).

There is no new safety information demonstrated in the two pivotal clinical trials with DR prednisone compared to immediate-release (IR) prednisone that has a well-characterized safety profile based on long-term post-marketing data. Currently, there are no REMS for any glucocorticoid product approved by the Agency.

The DRISK and the DPARP conclude that a REMS is not required and labeling will be adequate to mitigate the risks with use of the proposed DR prednisone formulation, if approved. (b) (4)
See **Section 4, Discussion**, in this review, for brief discussion of the rationale for the above conclusions.

1 INTRODUCTION

1.1 BACKGROUND

The NP01 formulation is a DR prednisone tablet-in-tablet dosage form consisting of a conventional IR prednisone core tablet surrounded by an inactive tablet shell. The applicant proposes a DR prednisone formulation (NP01) to optimize the efficacy of low-dose prednisone (≤ 5 mg daily) in the treatment of RA in adult patients.[2] (b) (4)
The proposed dosage strength range is consistent with currently marketed IR prednisone.

The IR prednisone, approved on June 28, 1974, has numerous generic products available on the US market. The drug substance in the DR and IR prednisone is the same; however, the DR formulation is different. Therefore, the applicant was required to evaluate the DR prednisone safety and efficacy in comparison to IR prednisone.

Proposed REMS

[1] Terminology: the applicant uses the term "modified-release" in their submission to describe the proposed DR prednisone formulation. The Agency uses the term "delayed-release" to define the proposed formulation that is the same as the IR prednisone with an outer coating to delay gastrointestinal absorption.

The applicant's proposed REMS includes a [redacted] (b) (4) (as stated in the **Executive Summary**). The applicant's focus in the proposed risk mitigation is [redacted] (b) (4)

European Union Approved Product

- December 2008: The Marketing Authorization application (MAA) for NP01 (Lodotra®) was recommended for approval through the European Union (EU) Decentralized Procedure (DCP) with Germany.
- March 2009: DR prednisone was approved in Germany and, subsequently, in 13 Member States for the treatment of RA in adults, especially when accompanied by morning stiffness. Product approval was based on a bridging PK study to the marketed IR prednisone (Study 005) and Phase 3 Study 003). See **Section 3.1 Overview of the Clinical Program,** in this review, for information about the studies in this submission.

1.2 REGULATORY HISTORY

The applicant submitted a 505(b)(2) application based on the US Reference Listed Drug (RLD) prednisone (PredniSONE Tablets United States Pharmacopeia (USP) Roxane Laboratories Inc., NDA 017109). The applicant was required to submit a relative bioavailability study comparing the DR prednisone to a listed product in the Orange Book, Decortin® 5 mg (Merck KGaA), an IR prednisone formulation marketed in Germany. Decortin 5 mg was shown to be equivalent to several US approved IR 5 mg tablets (e.g., Prednisone Watson Lab 5 mg Tablets).

The Agency's concerns were numerous including the different absorption profile of DR prednisone [redacted] (b) (4) compared with the IR product. The applicant was cautioned during the Pre-IND Meeting (March 24, 2006) that morning stiffness is not one of the measures of clinical efficacy in the American College of Rheumatology Criteria (ACR-20).

The Agency cautioned the applicant that to achieve a superiority claim, two adequate and well-controlled clinical studies will be required to support the proposed claim for relief of morning stiffness in patients with RA. The superiority claim for relief of morning stiffness compared 7 AM to 8 AM administration of standard IR prednisone with evening administration of DR prednisone.

Brief summary of the Regulatory Briefing for DR prednisone follows:

- May 18, 2012: The Agency held a Regulatory Briefing to discuss the potential claim for relief of morning stiffness in patients with RA and a possible indication in RA. Robert Temple supported the applicant's clinical development program (two clinical trials to achieve a claim). Only one of two pivotal trials supported

the proposed claim for relief of morning stiffness in RA. Due to numerous protocol violations and an unacceptable primary efficacy endpoint, the second study (foreign) failed to achieve statistically significant efficacy for DR prednisone.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

The following materials, listed by document date, were reviewed from 505(b)(2) NDA 202-020 for DR prednisone (Supplement 00) in regard to the proposed REMS:

- September 26, 2011: The applicant submitted NDA 202-020 with a proposed REMS. This NDA is under a standard 10-month review, Prescription Drug User Fee Act (PDUFA) Goal Date of July 26, 2012
- December 29, 2011: The applicant submitted proposed labeling for DR prednisone

2.2 ANALYSIS TECHNIQUES

The 505(b)(2) NDA for DR prednisone is reviewed in the context of a voluntarily submitted proposed REMS and whether or not a REMS should be required for a different formulation of prednisone, a product with a well-characterized, long-term safety profile and a class (glucocorticoids) that currently does not have any REMS.

3 RESULTS OF REVIEW OF A PROPOSED RISK EVALUATION AND MITIGATION STRATEGY FOR DELAYED-RELEASE PREDNISONE

3.1 OVERVIEW OF CLINICAL PROGRAM

The efficacy and safety data for the DR prednisone clinical development program submitted under NDA 202-020 (dated December 26, 2011) is composed of one PK study and two clinical trials:

- EMR 62215-005 (Study 005): Bridging PK study for IR prednisone
- EMR 62215-003 (Study 003): IND clinical study for the EU registration that had a different primary efficacy endpoint, improvement in morning stiffness, from the required US Phase 3 trial (See study 007 below).
- NP01-007 (Study 007): A multi-center, randomized (R), double-blind (DB), parallel group, placebo (PBO)-controlled study of NP01 (efficacy and safety) 5 mg DR prednisone and Disease Modifying Anti-rheumatic Drug (DMARD) versus PBO and DMARD for up to 12 weeks for the treatment of RA
    - A total of 350 patients (231 patients in the NP01 treatment group and 119 patients in the PBO group), randomized 2:1 to NP01 or PBO

Efficacy

The Agency did not accept efficacy data from Study 003 to support the effect of NP01 in the US-required NDA trial, Study 007. The primary efficacy endpoint was based on the

American College of Rheumatology (ACR) response criteria for 20% improvement (ACR20) in RA measures. Study 003, therefore, mainly served as a safety study.

Study NP01-007 demonstrated a statically significant increase in the ACR20 response of approximately 48% in the NP01 (5 mg) group versus 29% in the PBO group (p=0.0007; 95% CI 7.66, 28.22)

3.2 SAFETY CONCERNS

There are no new safety concerns identified in this NDA submission for DR prednisone different from the US RLD prednisone (PredniSONE Tablets, United States Pharmacopeia (USP), Roxane Laboratories Inc., NDA 017109). Neither of the two studies (007 and 003) were specifically powered to determine safety related to the NP01 delayed-release mechanism. See labeling for PredniSONE Tablets and the Warnings and Precautions Section.

The combined safety data (Study 007 and 003) included more than 1500 patients, an Agency requirement for a drug proposed for a chronic dosage regimen.

3.3 PROPOSED GOALS

(b) (4)

3.4 PROPOSED REMS ELEMENTS

(b) (4)

(b) (4)

C. Proposed Timetable for Submission of Assessments

(b) (4)

3.5 REMS Assessment Plan

(b) (4)

4 DISCUSSION

(b) (4)

The DRISK and DPARP agree that a REMS is not required to ensure that the benefits outweigh the risks of this drug. Therefore, a REMS is not required by the Agency for this proposed product, if it is approved. The rationale for this position is based on the fact that the moiety, Prednisone (IR), was approved by the Agency in 1974 and has a well-characterized, long-term safety profile with over 30 years post-marketing data. Currently, there is no required REMS for any FDA approved glucocorticoid product and/or indication.

Clinical safety data in the two required clinical studies with DR prednisone do not identify any new safety information. [redacted] The DR prednisone should be swallowed whole [redacted]. The tablet should not be broken, divided or chewed (in contrast to IR prednisone).

The DPARP will require the applicant to revise prednisone labeling to include pharmacokinetic (PK) data for DR prednisone that differs from approved IR prednisone PK data and include Chemistry Manufacturing and Control (CMC) information about composition of the outer-capsule of the DR prednisone product. A Medication Guide will not be required in revised labeling of prednisone.

5 CONCLUSION AND RECOMMENDATION

In conclusion, the DRISK has determined that a REMS for delayed-release prednisone tablets (1, 2, and 5 mg) submitted on September 26, 2011 under NDA 202020 is not necessary to ensure that the benefits outweigh the risks based on clinical safety data in this application. This conclusion is supported by the well-characterized safety profile of the moiety, prednisone (immediate-release), from long-term post-marketing safety data. The DRISK agrees that the Full Prescribing Information will be adequate to ensure that the benefits outweigh the risks with DR prednisone, if approved. Should new safety issues occur for this product or the class requiring further consideration of risk mitigation measures, send a consult to the DRISK.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CAROLYN L YANCEY

06/14/2012

NDA 202020 Prednisone Delayed-Release Tablets. A REMS is not required for this proposed product.

CLAUDIA B MANZO

06/15/2012

concur