CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202020Orig1s000

PHARMACOLOGY REVIEW(S)

INTEROFFICE MEMO

TO: NDA 202020
Sequence number/date/type of submission:
#001/September 26, 2011/original NDA

FROM: Molly E. Shea, Ph.D.
Interdisciplinary scientific Supervisor
Division of Pulmonary, Allergy and Rheumatology Products

DATE: June 25, 2011

NDA 202020 was submitted under the 505(b)(2) pathway for a modified release oral prednisone tablet (code name: NP01 and trade name: Rayos) on September 26, 2011. The original proposed indication was for the treatment of rheumatoid arthritis in adult patients. The indication was extended for all indications in the currently approved label in adults. No nonclinical studies were submitted or required for review to support the proposed clinical use. The sponsor (Horizon Pharma, Inc.) has relied on the previously approved prednisone labeling.

The nonclinical review of this NDA was focused on the sponsor's proposed labeling. Changes to the proposed labeling were recommended to be consistent with the currently approved products. The nonclinical labeling changes are included in Dr. Asoke Mukherjee's review dated June 22, 2012.

As there are no outstanding pharmacology/toxicology issues for this NDA application, the NDA may be approved pending labeling negotiations.

_____
Molly E. Shea, Ph.D.

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/s/

MOLLY E SHEA
06/25/2012
I concur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	202020
Supporting document/s:	SDN1
Applicant's letter date:	Sept 26, 2011
CDER stamp date:	Sept 26, 2011
Product:	Prednisone modified release tablet (NP01)
Indication:	Treatment of Rheumatoid arthritis in adult patient
Applicant:	Horizon Pharma Inc.
Review Division:	Division of Pulmonary, Allergy and Rheumatology Drug Products
Reviewer:	Asoke Mukherjee, Ph.D
Supervisor/Team Leader:	Molly Shea, Ph.D
Division Director:	Badrul Chowdhury, MD, Ph.D
Project Manager:	Michelle Jordan Garner

Template Version: December 7, 2009

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1 Executive Summary

1.1 Recommendations:

Prednisone is a synthetic corticosteroid prodrug that undergoes hepatic metabolism to form the active metabolite, prednisolone. Prednisolone inhibits the release of lipid and cytokine mediators of inflammation. The sponsor originally proposed the indication for the treatment of rheumatoid arthritis. However, upon review, the product is indicated for all conditions currently approved for reference listed drug.

1.1.1 Approvability

From a nonclinical point of view, the NDA is recommended for approval pending inclusion of the recommended changes to the nonclinical sections of the label.

1.1.2 Additional Non-Clinical Recommendations

No additional nonclinical study is recommended for the 505(b) (2) application. The revised recommendation to the label is shown below.

1.1.3 Labeling

Recommendations on labeling:

The sponsor submitted proposed labeling in general conformance with 21 CFR Parts 201, 314 and 601 Requirements on Content and Format of Labeling for Human Prescription Drugs and Biological Products and with Guidances for Industry on the Content and Format of Labeling for Human Prescription Drug and Biological products; Final Rule and Notices (January 24, 2006). The nonclinical changes to labeling are to conform to the most current CFR format (sections 8.1, 8.3, 11, 12.1 and 13.1) and the approved nonclinical label of prednisolone.

The non-clinical label recommended is shown below.

Reviewer's comment for the label change for pregnancy category:

Pregnancy category is changed from C to D as per recommendation of pediatric and Maternal Health Staff dated May 1, 2007. The Established pharmacological class of glucocorticoid is Corticosteroid. Therefore, glucocorticoid is replaced with corticosteroid as required for CFR 201.57. Also, NP01 is replaced by Rayos that is the trade name for the drug.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)

8.3 Nursing mothers

Reviewer's comment for nursing mothers:

The information on nursing is updated as recommended by the Pediatric and Maternal Health Staff dated June 4, 2012 based on the clinical information. The sponsor's proposed label was based on referenced 505(b) (2) drug and prednisolone which are immediate release formulations and therefore the previously approved label of prednisolone label indicated taking the medicine immediately after breast feeding to minimize the exposure of the drug to infants. Since Rayos has different

pharmacokinetic properties, the instruction for nursing in the proposed label required deletion as recommended below.

8.3 Nursing Mothers

(b) (4)

[redacted]

11 DESCRIPTION

Reviewer's comment for description of the drug: As mentioned earlier, glucocorticoid is replaced by the Established Pharamcological class, corticosteroids as required for CFR 201.57.

(b) (4)

[redacted]

12 CLINICAL PHARMACOLOGY

Reviewer's comments for mechanism of action: Glucocorticoid was replaced by corticosteroids as per CFR 201.57.

12.1 Mechanism of Action

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4)

[redacted]

13 NONCLINICAL TOXICOLOGY

Reviewer's comment for non-clinical toxicity: The proposed label was modified based on the approved label of prednisolone

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

1.2 Brief Discussion of Nonclinical Findings:

Rayos (NP-1) is a modified released corticosteroid formulation of prednisone, a pro-drug for prednisolone. It has anti-inflammatory effects in several disease conditions. No new nonclinical studies were required or submitted for review.

Corticosteroids have been used therapeutically for a variety of conditions since 1955. There was no new nonclinical data for prednisone or prednisolone presented by the sponsor.

The pregnancy category proposed by the sponsor for Rayos was Category C since this is the labeled pregnancy category for the approved reference product prednisone from Roxane laboratories. The issue of pregnancy category for prednisolone was previously consulted by the review division with The Pediatric and Maternal Health Staff (MHS) of Center for Drug Evaluation and Research (CDER) on June 4, 2007 for the appropriateness of pregnancy category C for prednisolone.

The review division also consulted with the MHT to evaluate the current label and provide advice if the labeling of corticosteroid was justified solely on the basis of published reproductive toxicity data in the animals when human data are now available. The MHS recommended that pregnancy category be changed to D for the label of prednisolone and other corticosteroid oral dosage forms based on available human data that indicated increased risks of orofacial clefts in pregnant women treated with corticosteroids. Based on the recommendations, pregnancy category D is now recommended for Rayos. The recommended label also adopted Established class of

prednisone as corticosteroid and the code name was replaced by the Trade name Rayos in the recommended label.

2 Drug Information

2.1 Drug

Modified release prednisone

2.1.1 CAS Registry Number (Optional)

53-03-2

2.1.2 Generic Name

Prednisone

2.1.3 Code Name

NP01

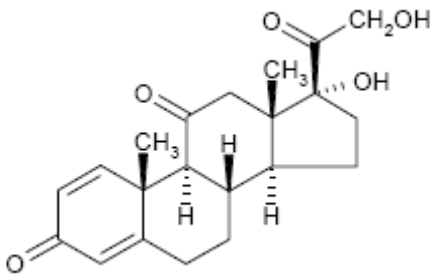
2.1.4 Chemical Name

17α,21-dihydroxypregna-1,4-diene-3,11,20-trione; 1,2-dehydrocortisone; 1,4-pregnadiene-17-alpha,21-diol-3,11,20-trione

2.1.5 Molecular Formula/Molecular Weight

$C_{21}H_{26}O_5$, Molecular weight 358.44

2.1.6 Structure



2.1.7 Established Pharmacologic class

Corticosteroid

2.2 Relevant IND/s, NDA/s, and DMF/s

IND 72,569, Lodotra (prednisone modified release tablet) , current sponsor is Horizon Pharma Inc. and original sponsor was Nitec Pharma for the indication of rheumatoid arthritis.

IND 105,868, Lodotra (prednisone modified release tablet) , current sponsor is Horizon Pharma Inc. and original sponsor was Nitec Pharma for the indication of bronchial asthma

The corporate name was changed from Nitec to Horizon Pharma as of April 1, 2010

2.3 Clinical Formulation

2.3.1 Drug Formulation

The sponsor has proposed three dosage oral forms of modified release prednisone as described below.

Table 1: Components and Composition of the NP01 Drug Product

Ingredient	Function	Amount per NP01 Tablet (mg)			% of NP01 Tablet (w/w)[3]		
		1 mg Tablet	2 mg Tablet	5 mg Tablet	1 mg Tablet	2 mg Tablet	5 mg Tablet
(b) (4)							

See above

2.3.2 Comments on Novel Excipients

There are no novel inactive ingredients for the proposed formulations. All inactive ingredients listed in the formulation are used in current FDA approved products. However, the amount of (b) (4) used for Rayos formulation was (b) (4) which exceeds that used in currently approved oral products up to (b) (4) The safety of (b) (4) at this level was discussed during a meeting on Dec 13, 2007 with the sponsor. The sponsor was informed that further nonclinical study for the safety of (b) (4) would not be required because (b) (4) is used under 21 CFR 184.1238 as a food additive without any specified limit. Therefore, use of the proposed amount in the current formulation is acceptable. .

2.3.3 Comments on Impurities/Degradants of Concern

There are no impurities or degradants for concern.

2.4 Proposed Clinical Population and Dosing Regimen

Rayos is proposed for the treatment of rheumatoid arthritis in adult patients. The modified release formulation will be administered at 5 mg once a day. The maintenance dose would be the lowest dose needed to maintain an adequate clinical response.

2.5 Regulatory Background

The sponsor submitted the NDA under section 505 (b) (2) of Food and Cosmetic Act for modified release prednisone at 1, 2 and 5 mg oral tablets. The sponsor referenced prednisone oral tablet marketed by Roxane lab as a reference drug ANDA 087800 for 1 mg tablet and ANDA 080352 for 5 mg tablet. The sponsor intends to rely on the previous findings of safety and efficacy for prednisone. The sponsor had a Pre-IND, End-of-Phase 2 and Pre-NDA meetings with the Agency on March 24, 2006, Dec 13, 2007 and Jan 26, 2010, respectively, for IND 72,569. No new nonclinical study for prednisone was recommended except qualifications of impurities of structural alert according to FDA 2008 guidelines on " Genotoxic and Carcinogenic impurities in Drug Substances and Products: Recommended Approaches" and ICH Q3 A (R)guidelines.

3 Studies Submitted

None

11 Integrated Summary and Safety Evaluation

Rayos (NP01) is a prednisone modified release tablet formulation proposed for the treatment of rheumatoid arthritis as a 505(b)(2) application referencing prednisone oral solution marketed by Roxane laboratories, ANDA 87800 and ANDA 80352. The non-clinical safety of the prednisone modified release tablet is based on the previously approved safety of the referenced product. The sponsor did not did not submit any new nonclinical safety data for the 505(b)(2) application. The approved label for prednisolone was also used to support safety since prednisone is converted to the active form prednisolone by liver metabolism.

The extended release formulation does not contain any novel excipients, except (b) (4) was used in previously approved products in the amount similar or lesser than that used in the formulation. Since (b) (4) is used as a food additive at higher amount, its safety at the proposed level is known. Therefore, the use of (b) (4) at the proposed amount does not have additional safety concerns.

Since the clinical safety of prednisone is already established, no new nonclinical toxicity data for Rayos formulation was required for the application. The pharmacologically active metabolite of prednisone is prednisolone. Prednisolone's mechanism of action is similar to the physiological actions of endogenous corticosteroids. These effects are gluconeogenesis, increased deposition of glycogen in the liver, inhibition of glucose utilization, anti-insulin activity, increased catabolism of protein, lipolysis, synthesis and storage of fat, increased glomerular filtration rat and increase excretion of urate and calcium. Prednisolone inhibits inflammatory process and later stages of wound healing. Prednisolone can stimulate secretion of various components of gastric juice. Prednisolone, as with other corticosteroids, can feedback on the brain and pituitary gland to suppress of the production of corticotrophin (ACTH) and its releasing factor to suppress endogenous corticosteroid secretion. Prednisolone also has slight mineralocorticoid activity on kidney stimulating sodium retention and loss of potassium that may lead to hypertension. The major alteration to the sponsor's label was the change in pregnancy category from a "C" to a "D," based on the risk and benefits to pregnant women as recently recommended for all corticosteroid labels by the Pediatric and Maternal Health Staff, CDER, FDA. The reviewer also recommended that "glucocorticoid" should be replaced by "corticosteroid" based on the established pharmacological class recommended for prednisone.

Based on the review of the nonclinical data, label and inactive ingredients used in the formulation, there are no further nonclinical safety concern for the approval of the product. The NDA can be approved from the nonclinical point of view.

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/s/

ASOKE MUKHERJEE
06/22/2012

MOLLY E SHEA
06/22/2012
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA202020

NDA/ Number: 202020 **Applicant: Horizon Pharma Inc** **Stamp Date: Sept 26, 2011**

Drug Name: Prednisone (NP1) **NDA/BLA Type: 505(b)2**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		As a 505b2, the sponsor is providing support for their drug product formulation for the oral route of administration. No new non-clinical organ system toxicity conducted because requirement for non-clinical bridging toxicity was waived.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		No non-clinical organ system toxicity conducted. The non-clinical toxicity to prednisone is well known and as a 505b2 the sponsor is supporting this route of administration.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	x		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA202020

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	x		Impurity issue for [redacted] (b) (4) is addressed and the level set for [redacted] (b) (4) of the drug product. The sponsor would minimize [redacted] (b) (4) during the storage.
11	Has the applicant addressed any abuse potential issues in the submission?	NA	NA	Not applicable (NA) or required for prednisone.
12	If this NDA/BLA is to support an Rx to OTC switch, have all relevant studies been submitted?	NA	NA	This will be a prescription product

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _____Yes_x__

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

ASOKE MUKHERJEE
11/14/2011
Pham/Tox NDA filing check list

MOLLY E TOPPER
11/14/2011
I concur.