

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202020Orig1s000**

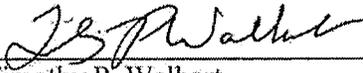
**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

Paragraph I Certification for Prednisone

Prednisone is currently listed in the FDA Orange Book as the reference listed drug (RLD) for prednisone tablets (New Drug Application [NDA] 017109 held by Roxane Laboratories).

Horizon Pharma, Inc.'s 505(b)(2) application intends to rely on the FDA's previous findings of safety and efficacy for prednisone.

Patent Certification: "Paragraph I Certification": I, on behalf of Horizon Pharma, Inc. certify that patent information has not been submitted to the FDA for prednisone.



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Timothy P. Walbert  
Horizon Pharma, Inc.  
Chairman, President and Chief Executive  
Officer

July 25, 2012

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Date

## EXCLUSIVITY SUMMARY

NDA # 202020

SUPPL #

HFD # 570

Trade Name RAYOS

Generic Name prednisone (delayed release)

Applicant Name Horizon Pharma

Approval Date, If Known

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The application is supported by CMC and data from bioavailability trials linking RAYOS to an approved formulation of prednisone, for which safety and efficacy are already established. The clinical efficacy and safety trials that were conducted for the program were not necessary to support the safety and efficacy of RAYOS.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 17109 (PredniSONE) this product was discontinued

NDA# 009766 (Meticorten)this product was discontinued

NDA# There are dozens of other approved prednisones, some discontinued and some are still marketed

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

The CMC information and data from the bioavailability trials are adequate to support approval.

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO



YES   
Explain:

!  
! NO   
! Explain:

Investigation #2

YES   
Explain:

!  
!  
! NO   
! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

=====

Name of person completing form: Michelle Jordan Garner  
Title: RPM  
Date: 7/16/12

Name of Office/Division Director signing form: Badrul A. Chowdhury  
Title: Director, DPARP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MICHELLE Y JORDAN GARNER  
07/27/2012

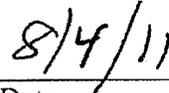
BADRUL A CHOWDHURY  
07/27/2012

**1.3.3 Debarment Certification**

Horizon Pharma, Inc. certifies that we did not and will not use the services in any capacity of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



\_\_\_\_\_  
Timothy P. Walbert  
Chairman, President, and Chief Executive Officer  
Horizon Pharma, Inc.



\_\_\_\_\_  
Date

MEMORANDUM

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

**DATE:** July 25, 2012

**TO:** Badrul A. Chowdhury, MD, PhD  
Director, DPARP

**FROM:** Michelle Jordan Garner, MS, OTR/L  
Senior Regulatory Management Officer

**SUBJECT: Regulatory Briefing (May 18, 2012) for Prednisone Regulatory Pathway  
Direction**

**APPLICATION/DRUG:** NDA 202020/Rayos (delayed-release prednisone tablets)

**Background:**

Prednisone is a synthetic corticosteroid approved for multiple indications, including the treatment of rheumatoid arthritis (RA). Horizon Pharma has conducted a clinical development program for a new delayed-release formulation of prednisone (Rayos), proposed for the treatment of RA in adults. Since prednisone already has an indication for the treatment of RA, CMC and clinical pharmacology data would generally be adequate for a new formulation of prednisone. However, the Applicant conducted a clinical trial to support the proposed RA indication with a reduction in morning stiffness as a novel secondary labeling claim based on the Agency's advice given in 2006 and 2007. Other than the previously known differences in pharmacokinetics, the application does not include any data to suggest that Rayos has a clinically meaningful difference compared to immediate-release prednisone.

This meeting was scheduled so that the regulatory briefing panel could 1) suggest the appropriate regulatory approval and labeling pathway, between the options of a) approving with a unique label specific for an RA treatment indication or b) approving with labeling for all of the indications for immediate-release prednisone; and 2) discuss the need for pediatric studies in the context of the two options. See attachment 1 for slides presented at this meeting.

### **Questions:**

1. The application includes new CMC, clinical pharmacology, and clinical trial information. Based on the review to date, the CMC and clinical pharmacology data alone appear sufficient to support approval of Rayos. Is the following appropriate:
  - a. Approval with a specific carve-out indication for rheumatoid arthritis, including new clinical trial data (ACR20 response rates from Trial 007) in the label.
  - b. Approval with the multiple indications currently approved for prednisone IR.
2. As a new dosage form, Rayos triggers pediatric studies under PREA. In light of the issues raised in Question #1, Is it reasonable to require pediatric studies for Rayos?

### **Discussion:**

Dr. Temple stated that this meeting was for discussion purposes only and should not be viewed as a decision-making forum.

Questions were raised regarding the validity of the morning stiffness endpoint. DPARP responded that they questioned the validity of the morning stiffness endpoint because morning stiffness is very difficult to assess in view of its variable nature and insensitivity to change due to its subjectiveness. Additionally, the use of therapeutic biologic agents and DMARDs has resulted in morning stiffness being reported by patients who have not been adequately treated or only early in their disease course. Therefore, the clinical usefulness of morning stiffness in assessing RA response to treatment has markedly diminished.

Regarding the requirement for pediatric studies under PREA, Dr. Lisa Mathis (Associate Director, Pediatric and Maternal Health Staff) stated that one needs to look at the criteria for waiving pediatric studies. She stated that if the product is not likely to be used in a significant number of pediatric patients, and does not provide a therapeutic benefit over other products, the need to conduct pediatric studies may be waived with the necessary supportive data. Alternatively, existing data from IR prednisone may be adequate to label Rayos for pediatric use without further pediatric study.

Based on the presentations, the panel generally agreed that CMC and clinical pharmacology data would be sufficient to support Rayos's efficacy as a treatment for RA. The merit of including new placebo-controlled clinical trial data for the ACR20 endpoint in the label was debatable given the long-accepted efficacy of prednisone for the RA indication. In terms of the morning stiffness data, the panel thought that these results may warrant inclusion in the label provided there was adequate evidence to support the claim as well as the instrument used to assess it. If not, the panel generally recommended that the drug be approved with the same generalized indications and labeling as the reference drug. In terms of the requirement for pediatric studies, the panel stated that it was reasonable to conclude that further pediatric studies were not required given the long history of prednisone use in pediatric populations, provided that no new claims were approved for the product.

# **NDA 202020**

## **Delayed Release Prednisone Tablet**

**Proposed Indication: Treatment of Rheumatoid Arthritis**

CDER Regulatory Briefing  
May 18, 2012

Division of Pulmonary, Allergy and Rheumatology Products

## Review Team

- Joan Buenconsejo
- Ruthanna Davi
- Suresh Doddapaneni
- Michelle Jordan Garner
- Kiya Hamilton
- Ping Ji
- Susan Limb
- Rosemarie Neuner
- Prasad Peri
- Alan Schroeder
- Xiaobin Shen

## NP01

- Prednisone delayed-release tablet (1, 2, and 5 mg)
- Proposed indication: Treatment of rheumatoid arthritis in adult patients
- Proposed inclusion of multiple secondary endpoints including relief of morning stiffness in label

# Objective of Regulatory Briefing

- Seek input regarding
  - Suitable regulatory approval pathway
  - Appropriate labeling indication
  - Need for pediatric studies

# Outline of Presentation

- Clinical
  - Overview of rheumatoid arthritis and patient reported outcome of morning stiffness
  - Historic overview of glucocorticoids
  - Background regulatory history of delayed release prednisone
  - Overview of clinical trials conducted in support of delayed release prednisone in RA
- CMC
- Clinical Pharmacology
- Pediatric Issues
- Possible Approval Actions for Consideration
- Questions for discussion

# Rheumatoid Arthritis (RA)

- Chronic, systemic inflammatory disease
  - Symmetrical, erosive synovitis that may include extra-articular involvement
  - Variable course may result in significant joint destruction, disability and increased mortality despite therapy
- 1987 ACR classification criteria for RA
  - $\geq 4$  of following must be present:
    - Morning stiffness, arthritis in  $\geq 3$  joints, arthritis of hand joints, symmetric arthritis, rheumatoid nodules, presence of rheumatoid factor and radiographic changes
- 2010 ACR/EULAR RA criteria no longer include morning stiffness
  - Patient reported outcome of morning stiffness lacks discriminatory capability
    - Inflammatory vs noninflammatory disease
    - Treated vs untreated RA

# RA Outcomes and Morning Stiffness

- ACR20
  - Current US regulatory standard EP for RA studies
  - Composite index based on  $\geq 20\%$  improvement in tender and swollen joint count as well as  $\geq 20\%$  improvement in 3 of the following 5 parameters:
    - Patient pain assessment, patient global assessment, physician global assessment, patient self-assessed disability (HAQ), and elevated ESR or CRP
- Disease Activity Score (DAS)
  - Current European regulatory standard EP for RA studies
  - Composite index score
    - # tender and swollen joints based on 28 joint count, ESR/CRP, and patient's global disease assessment
    - Score range 0-10; higher score consistent with higher disease activity
- Morning stiffness **not included** in ACR20 or DAS due to
  - Variable nature **and**
  - Insensitivity to change due to subjectiveness

# Historic Overview of Glucocorticoids

- First used by Hench at the Mayo Clinic to successfully treat a patient with RA in 1948
  - Hench and colleagues awarded Nobel Prize for Medicine in 1950
- Now widely used to treat autoimmune diseases and other diseases associated with an inflammatory component
- Clinical usefulness offset by:
  - Serious side effects
    - Cushing syndrome, osteoporosis, Type 2 DM, truncal weight gain, glaucoma, cataracts and CNS effects (insomnia, mood disruptions, and memory impairment)
  - Introduction of triple drug therapy and therapeutic biologics for the management of RA
    - Better disease and symptomatic control

# Historic Overview of Glucocorticoids

- Prednisone
  - Immediate release oral formulation commercially available since mid-1960s
  - Widely available as a generic drug
  - Approved indication for RA as per RLD label (Roxane Labs NDA 17109 PredniSONE Tablets USP):

*“As adjunctive therapy for short-term administration or low-dose maintenance therapy of rheumatoid arthritis including juvenile rheumatoid arthritis”*
  - Indication is non-specific in keeping with glucocorticoids’ broad reaching immunosuppressive and anti-inflammatory effects

# Background

- NP01
  - Delayed release formulation of prednisone
    - Comprised of core prednisone tablet within an inactive shell
    - Designed to release prednisone during the middle of the night following bedtime dosing to shift concentration time curve of IR prednisone by 4 hours
  - “Chronotherapy” for morning stiffness in RA
    - Symptoms of AI diseases such as RA exhibit circadian rhythms as a result of elevated levels of pro-inflammatory cytokines resulting in worse joint pains and stiffness in AM
    - Postulated delayed drug release optimizes drug effect during early morning disease exacerbations resulting in a decrease in symptoms such as morning stiffness without compromising compliance

## Regulatory History: PreIND Meeting (2006)

- 505(b)(2) pathway discussed
- [REDACTED] (b) (4)
- Limitations of ongoing European study (EMR62215-003)
  - Multiple design problems: integrity of blind, assessment of AM stiffness, evaluation of duration of drug effect over 24 hours, minimum threshold for disease activity, etc...
  - Disagreement within division regarding the validity of [REDACTED] (b) (4) morning stiffness claim in view of the current therapeutic advances in RA
- Sponsor advised to conduct a new study using standard EP (ACR20) and evaluate morning stiffness as secondary outcome
  - Needed to provide exposure data in US population

## Regulatory History: EOP2 meeting (2007)

- Prior advice to conduct an additional clinical trial reiterated
  - Labeling claim for morning stiffness could be considered if both the European and US clinical trials supported efficacy
  - Persistent internal disagreement within the division regarding claim's validity

## Regulatory History: PreNDA Meeting (2010)

- Morning stiffness claim revisited
  - Limited to RA
  - May be described in clinical studies section but not included in the indication statement
- PRO guidance referenced and sponsor advised to submit validation and justification of the instrument
  - EP lacked definitions for resolution of morning stiffness and recurrence of stiffness to be used by patients to answer the question consistently
  - Also lacked information to support:
    - Reliability **and**
    - Construct validity of EP
- NDA submission did not include any scientific justification for a responder definition, or discussion regarding translation or cultural adaptation of EP

## Efficacy Studies

Study	Design	N	Dose Regimen	End Point
<b>NP01-007 (U.S.)</b>	12 Wk, P3, MC, R, DB, PC, parallel group study in RA patients on DMARDs <sup>a</sup>	231 119	5 mg NP01 QPM Placebo	1 <sup>0</sup> : ACR20  2 <sup>0</sup> : Duration of AM stiffness
<b>EMR622 15-003 (EU)</b>	3-month, P3, MC, R, DB, AC, double dummy, parallel group study in RA patients on DMARDs <sup>a</sup> with 9-month OLE	144 144	3-10mg/d NP01 QPM (10 pm) 3-10mg Decortin QAM (6-8 AM)  OLE: NP01 3-10 mg/d	1 <sup>0</sup> : Duration of AM stiffness  2 <sup>0</sup> : DAS 28 and other endpoints

<sup>a</sup>Both studies prohibited concomitant use of biologic agents

## Study NP01-007 Primary and Key Secondary Efficacy Results (mITT Population)

Primary Endpoint- ACR20 Response at Visit 4						
Imputation scheme	NP01 n/N (%)	Placebo n/N (%)	% Difference in proportions (95% CI)		Odds Ratio (95% CI)	P-value
Worse Case	108/231 (46.8%)	34/119 (28.6%)	18.2	17.4 (7.2, 27.6)	2.25 (1.4, 3.6)	0.0010
Key Secondary Endpoint- Relative Change from Baseline in the Duration of Morning Stiffness at Visit 4						
Imputation scheme	Relative Change (%)				Difference in median [%] (95% CI)	P-value
	NP01		Placebo			
	N	Median	N	Median		
LOCF	230	-54.2	119	-28.6	-20.8 (-32.5, -7.6)	0.0006
BOCF	231	-51.4	119	-24.6	-18.7 (-31.3, -6.0)	0.0011

*Table courtesy of Dr. Kiya Hamilton*

## Study EMR 62215-003 Primary and Secondary Efficacy Results (ITT Population)

### Primary Endpoint -Duration of Morning Stiffness at Week 12

Imputation scheme	Relative Change (%)				Treatment Difference LS mean (SE) [%] Lower limit of 95% CI	P-value (one-sided)
	NP01		Decortin			
	N	Median	N	Median		
LOCF	125	-22.6	129	-0.3	22.4 (11.1) 0.5	0.0226

### Secondary Endpoints DAS28

Assessment	NP01 n/N (%)	Decortin n/N (%)
DAS28 Relative change	136/144 -9.0 (17%)	137/144 -12.3 (17%)

## Summary of Efficacy Data Supporting NP01

- Placebo-controlled Study NP01-007
  - Demonstration of efficacy based on ACR20 expected
  - Clinical relevance of improvement in morning stiffness is questionable
    - Validity of morning stiffness claim in question
    - Nonvalidated PRO instrument
- Active-controlled Study EMR 62216-003
  - Clinical relevance of morning stiffness claim again questionable
  - Study not designed to demonstrate superiority of NP01 over prednisone IR for overall treatment of RA

# CMC

3 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/ucm071666.htm>

The screenshot shows the FDA website interface. At the top, there is a navigation bar with the FDA logo and the text 'U.S. Food and Drug Administration Protecting and Promoting Your Health'. To the right of the logo, there are links for 'A to Z Index', 'Follow FDA', and 'Subscribe to Emails', along with a search bar and a 'SEARCH' button. Below the navigation bar, there is a horizontal menu with buttons for 'Home', 'Food', 'Drugs', 'Medical Devices', 'Vaccines, Blood & Biologics', 'Animal & Veterinary', 'Cosmetics', 'Radiation-Emitting Products', and 'Tobacco Products'. The main content area is titled 'Drugs' and includes a breadcrumb trail: 'Home > Drugs > Development & Approval Process (Drugs) > Forms & Submission Requirements'. On the left side of the main content area, there is a blue button labeled 'Development & Approval Process (Drugs)'. The main heading is 'Dosage Form', followed by the text 'FDA Data Element Number. None.'. Below this is a table with the following data:

NAME	DEFINITION	USE RESTRICTIONS	SHORT NAME	FDA CODE	NCI CONCEPT ID
TABLET, DELAYED RELEASE	A solid dosage form which releases a drug (or drugs) at a time other than promptly after administration. Enteric-coated articles are delayed release dosage forms.	a,b,c	TAB DR	520	C42905

Per CDER Data Standards Manual, the product is a **delayed release tablet**.



# Clinical Pharmacology

# Outline

- Background
- Review of clinical pharmacology program
- Summary

# Prednisone Products

- No US-approved modified release prednisone products

Drug Products	Strength, Formulation	Dosage and Administration
PredniSONE	1, 2.5, 5, 10, 20, 50 mg Tablet  5 mg/5 mL, 5 mg/mL Solution	<ul style="list-style-type: none"> <li>•It is recommended that prednisone be administered in the morning prior to 9 am.</li> <li>•Gastric irritation may be reduced if taken before, during, or immediately after meals or with food or milk.</li> <li>•The initial dosage of prednisone may vary from 5 mg to 60 mg per day, depending on the specific disease entity being treated.</li> </ul>
NP01	1, 2, 5 mg Tablet	<ul style="list-style-type: none"> <li>•NP01 should be taken daily <span style="background-color: #cccccc; padding: 2px;">(b) (4)</span></li> <li>•Initial dose: NP01 5 mg ad <span style="background-color: #cccccc; padding: 2px;">(b) (4)</span> day at bedtime.</li> <li>•Maintenance dose: Use lowest dosage that will maintain an adequate clinical response.</li> </ul>

## Prednisone General PK Properties

- **Absorption:**
  - Systemic bioavailability: 80-100%
  - T<sub>max</sub>: 1-2 h
  - Food may prolong T<sub>max</sub>, but has no effect on bioavailability
- **Metabolism:**
  - Prednisone is completely converted to its active metabolite prednisolone
  - Plasma levels of prednisolone are four- to ten-fold higher than those of prednisone.
- **Elimination:**
  - T-half: 2-3 h for prednisone and prednisolone
  - With once daily dosing, concentrations are negligible at the end of the dosing interval

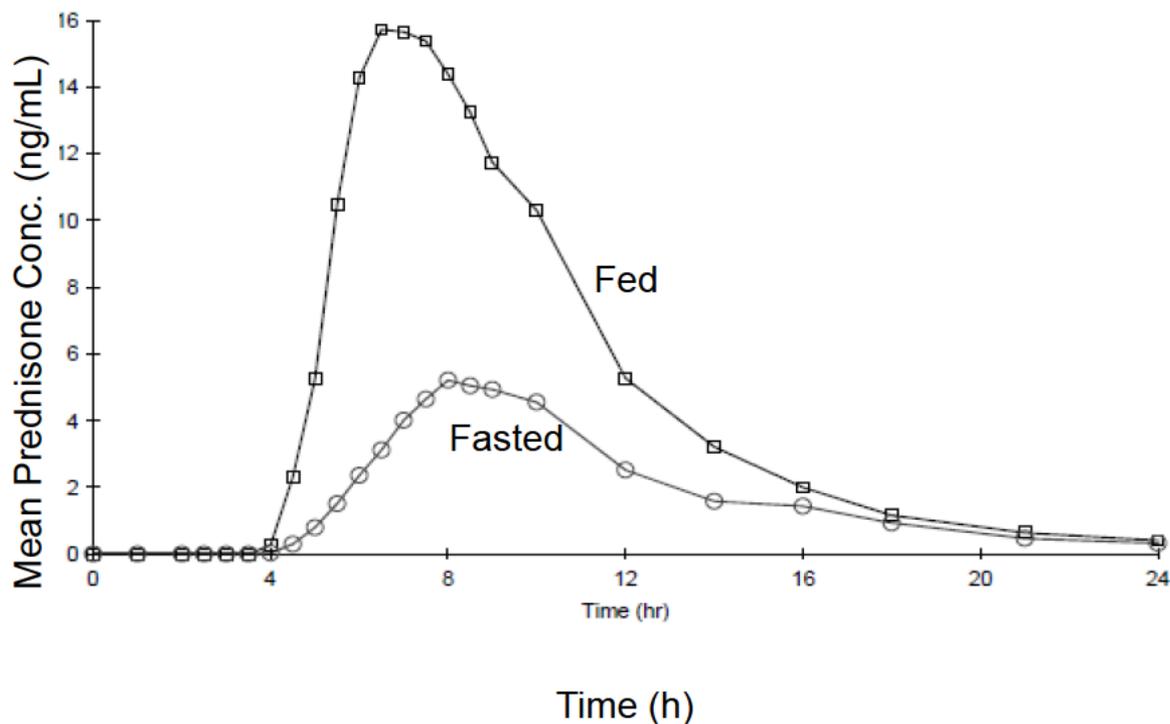
## Clin Pharm Program

- **Food effect**
- **Relative bioavailability**
- Dose proportionality
  - 1, 2, and 5 mg tablets are dose-proportional
- Site-change BE assessment
  - BE demonstrated

# Food Effect Study (NP01-006)

- **Methodology:** Open-label, randomized, single oral dose, two-way crossover
- **Treatments:**
  - Reference: DR tablet 5 mg given fasted (Treatment A)
  - Test: DR tablet 5 mg given with HFM (Treatment B)
- **Subjects:** Healthy subjects (18-50 years of age), n=24

# Mean Prednisone Plasma Profiles (Study NP01-006)



Exposure decreases and T<sub>max</sub> increases under fasting conditions for DR tablet formulation.

## Pharmacokinetic Summary (Study NP01-006)

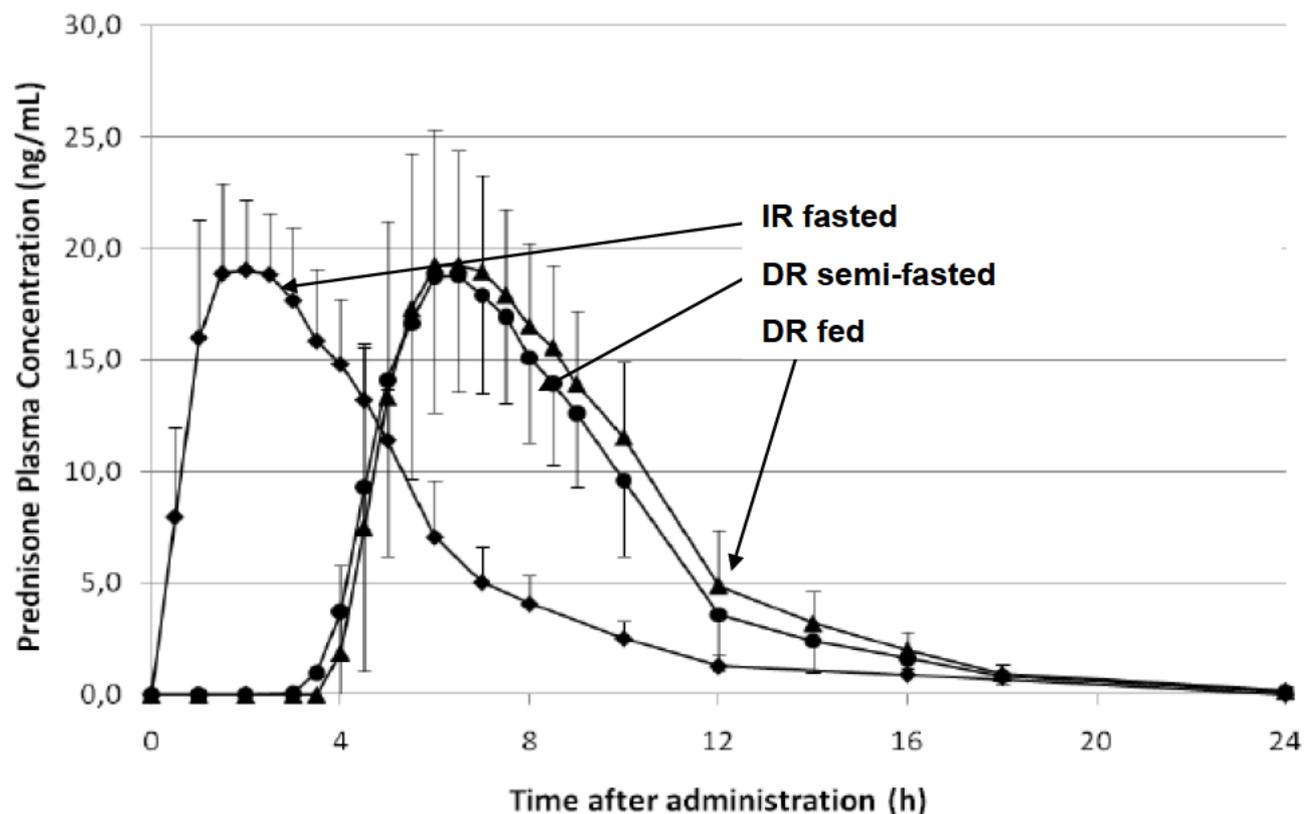
	<b>Prednisone</b>	
<b>Treatment</b>	<b>DR Fasted</b>	<b>DR Fed</b>
<b>C<sub>max</sub> (ng/mL)</b>	6.6 (56%)	19 (17%)
<b>AUC<sub>0-t</sub> (ng h/mL)</b>	34 (64%)	101 (19%)
<b>T<sub>max</sub> (h)</b>	8.4 (6-18)	6.9 (5.5-10)

AUC and C<sub>max</sub> decrease by about 60% under fasting conditions

## Relative Bioavailability Study Design (Study EMR62215-005)

- **Methodology:** Open-label, randomized, single oral dose, 3-way crossover
- **Treatments:**
  - **Reference:** IR tablet 5 mg given at 02:00 am fasted (Treatment A)
  - **Test:** DR tablet 5 mg given at 20:00 pm fed with normal dinner at 19:30 pm (Treatment B)
  - **Test:** DR tablet 5 mg given at 20:00 pm semi-fasted with light meal at 17:30 pm (Treatment C)
- **Subjects:** Healthy subjects (18-50 years of age), n=27

# Mean Prednisone Plasma Profiles (Study EMR 62215-005)



DR formulation has a delayed T<sub>max</sub> of ~4 hours as compared to IR formulation.

# Pharmacokinetic Summary (Study EMR 62215-005)

	<b>Prednisone</b>		
<b>Treatment</b>	<b>IR Fasted</b>	<b>DR Semi-Fasted</b>	<b>DR Fed</b>
<b>C<sub>max</sub> (ng/mL)</b>	21.1 (17%)	21.4 (26%)	22.2 (16%)
<b>AUC<sub>0-t</sub> (ng h/mL)</b>	108 (15%)	114 (27%)	124 (20%)
<b>T<sub>max</sub> (h)</b>	2 (1.0-4.0)	6.0 (4.5-10)	6.5 (4.5-9)

Similar C<sub>max</sub> and AUC between DR taken under fed conditions and IR taken under fasting conditions.

## Summary

- NP01 has a substantial food effect
  - Bioavailability decreases by about 60% in fasting state
- NP01 administered under fed conditions has similar bioavailability as compared to the immediate release tablet.
- NP01 has a delayed T<sub>max</sub> of ~4 hours as compared to IR formulation.
  - Otherwise the profiles are super imposable

## Pediatric Issues for Consideration

- NP01 as a new dosage form triggers PREA
- Immediate release formulation of prednisone is approved for JIA
- No clinically important differences in both efficacy and safety observed in the two studies conducted in adults with RA
- DPARP's assessment is that the pediatric requirement can be considered fulfilled

## Possible Regulatory Actions for Consideration

- Approval for a general RA indication with a unique label
  - Inclusion of relevant clin pharm data
  - May result in exclusivity given inclusion of new clinical data in the label (ACR20 results +/- morning stiffness data and other secondary outcomes)

**OR**

- Approval for all the same indications currently approved for prednisone IR with same labeling as current RLD
  - No new clinical data in the Clinical Studies section
  - Inclusion of relevant clin pharm data

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## Panel Questions

1. The application includes new CMC, clinical pharmacology, and clinical trial information. Based on the review to date, the CMC and clinical pharmacology data alone appear sufficient to support approval of NP01. Please comment on the appropriateness of the following:
  - a. Approval with a specific carve-out indication for rheumatoid arthritis, including new clinical trial data in the label.
  - b. Approval with the multiple indications currently approved for prednisone IR.
  
2. As a new dosage form, NP01 triggers pediatric studies under PREA. In light of the issues raised in Question #1, please comment on whether it is reasonable to require pediatric studies for NP01.

# Parting Thoughts...

## My Uncle Terwillinger on the Art of Eating Popovers

*By Dr. Seuss*

*Commencement speech at Lake Forest College June 1977*

My uncle ordered popovers  
from the restaurant's bill of fare.  
And, when they were served, he regarded them  
with a penetrating stare...  
Then he spoke great words of wisdom  
as he sat there on that chair:  
"To eat these things", said my uncle,  
'you must exercise great care.  
You may swallow down what's solid  
But...you must spit out the air!'  
And as you partake of the world's bill of fare,  
That's darned good advice to follow.  
Do a lot of spitting out the hot air.  
And be careful what you swallow."



# Back-Up Slides

## Study EMR 62215-003 Primary and Secondary Efficacy Results (ITT Population)

### Primary Endpoint -Duration of Morning Stiffness at Week 12

Imputation Scheme	Relative Change (%)				Treatment Difference LS mean (SE) [%] Lower limit of 95% CI	P-value (one-sided)
	NP01		Decortin			
	N	Median	N	Median		
LOCF	125	-22.6	120	-0.3	22.4 (11.1) 0.5	0.0226

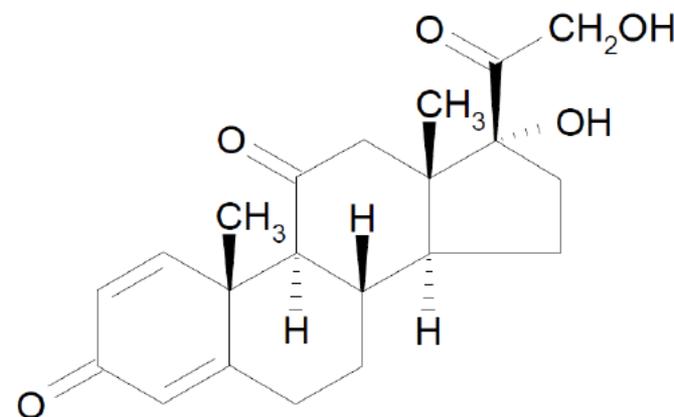
### Secondary Endpoints DAS28 and ACR20<sup>a</sup>

Assessment	NP01 n/N (%)	Decortin n/N (%)
DAS28	136/144	137/144
Relative change	-9.0 (17%)	-12.3 (17%)
ACR20 <sup>a</sup>	21/144 (15%)	25/144 (17%)

<sup>a</sup>ACR20 conducted as post hoc analysis

## Prednisone Drug Substance

- White to almost white crystalline powder.
- $C_{21}H_{26}O_5$ .
- 358.44 g/mol.
- Very slightly soluble in water at 37°C.
  - Tianjin Tianyao Pharm. Co.
  - Tianjin, China
  - DMF (b) (4)



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MEETING ATTENDEES

Date: May 18, 2012      Time: 11am -1:00 p.m.      Place: White Oak CSU, Room 2047

Type of meeting: Regulatory Briefing – NDA 202020 Delayed-release Prednisone  
Indicated for the treatment of rheumatoid arthritis

NAME (please print)	SIGNATURE	TITLE	REPRESENTING
Susan Limb	(b) (6)	MO TL	DPARP
Nichelle Rashid	(b) (6)	OSE RPM	OSE
Sandy Barnes	(b) (6)	CPMS	DPARP
Courtney Suggs	(b) (6)	RPM	PMHS
Deborah Seibel	(b) (6)	MO	DPARP
Alan Schroeder	(b) (6)	CMC Lead	ONDA
Molly Hill	(b) (6)	PT Sup	DPARP
Joan Buenconsejo	(b) (6)	stats	<del>DPARP</del> OB
Sarah Yim	(b) (6)	MO	DPARP
RICHARD AZIDUR	(b) (6)		DHDP
SWEZANA TRAJKOVIC	(b) (6)	MO	DDDP
ERIC DUFFY	(b) (6)	Dir -	ONDA
CHRISTINA BURKH	(b) (6)	MO	DPP
NIKUNTS PATEL	(b) (6)	PT reviewer	DPARP
Charles Jewell	(b) (6)	Chemist	ONDA
R Temple	(b) (6)	Dep Div ODER	ODER office
Obenls Wu	(b) (6)	pho	OGIEP
RIMA BEM	(b) (6)	Math. stat	OB
Carol Hill	(b) (6)	RPM	DPARP
James Stansbury	(b) (6)	CSO	SEALD

MEETING ATTENDEES

Date: May 18, 2012      Time: 11am -1:00 p.m.      Place: White Oak CSU, Room 2047

Type of meeting: Regulatory Briefing – NDA 202020 Delayed-release Prednisone  
Indicated for the treatment of rheumatoid arthritis

NAME (please print)	SIGNATURE	TITLE	REPRESENTING
Ladan Jafari	(b) (6)	CPMS/DPARP	
Kiya Hamilton		Math Stat	
AUSTIN CHHEU		CLIN PHARM FELLOW	
Nikolay Nikolov		MO/DPARP	
Kathleen Fritsch		Biosci	
Saret Maynard		MO/DPARP	
VICKI KUSIAK		Dep. Dir ODE III	ODE III
Teena Thomas		OSE/OPM	DPARP
Julie Beitz		Director	ODE III
Iris Masucci			OMP
Antonia Dow		Pharmacologist	
Wiley Chambers		Dep Dir Director	DTOP
A DURNOWICZ		Team Leader	DPARP
B. E. H. H. H. H.		Pharmacologist	DLIEP
Suchitra Reddy		MO/DMEP	
Hon-Sum Ko		Medical Officer	DDDP
LORENZO Rocca		chemist	ONDQA
Maria Allende		Physician-M.O.	OND-DAIP
Eileen Navarro		M.O.	OND-DAIP
Christina Nguyen		MO	OND-DAIP

**MEETING ATTENDEES**

Date: May 18, 2012      Time: 11am -1:00 p.m.      Place: White Oak CSU, Room 2047

Type of meeting: Regulatory Briefing – NDA 202020 Delayed-release Prednisone  
Indicated for the treatment of rheumatoid arthritis

NAME (please print)	SIGNATURE <i>(b) (6)</i>	TITLE	REPRESENTING
Lucile Yang	<i>(b) (6)</i>	MO	DMIP
John Torrici	<i>(b) (6)</i>	M.D.	DGIEP
Kachi Illoh	<i>(b) (6)</i>	MD	DNP
Kim Lawrence	<i>(b) (6)</i>	RMA	DRISK
Marc Cavaille-Gil	<i>(b) (6)</i>	M.O.	DTOP
Jean Nashed	<i>(b) (6)</i>	Chemist	ONDQA
Ira Threlton	<i>(b) (6)</i>	MD	DMIP
Karen Riviere	<i>(b) (6)</i>	Ph.D.	ONDQA
MINERVA Hughes	<i>(b) (6)</i>	Ph.D	ONDQA
Lisa Mathus	<i>(b) (6)</i>	MD	PMAS
Doug Throckmorton	<i>(b) (6)</i>	MD	CDER 10

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MICHELLE Y JORDAN GARNER  
07/26/2012

### 505(b)(2) ASSESSMENT

Application Information		
NDA # 202020	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: RAYOS (NP01) Established/Proper Name: prednisone (modified-release) Dosage Form: tablets Strengths: 1mg, 2mg, 5mg		
Applicant: Horizon Pharma, Inc.		
Date of Receipt: 9/26/11		
PDUFA Goal Date: 7/26/12	Action Goal Date (if different):	
Proposed Indication(s): Rheumatoid Arthritis in adults		

### GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
<b>PredniSONE</b> NDA 17109	Label Sections: 2.1, 4, 5.1-9, 5.12, 5.13, 6.2, 7.2, 7.10, 8.1, 8.3, 8.5, 12.1, MedGuide
<b>Literature</b>	Label Sections: 8, 13.1

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

*Horizon demonstrated BE to an immediate-release prednisone formulation approved in the EU (Decortin, marketed by Merck KG, Darmstadt, Germany). FDA had previously agreed that their in vitro data could be used to bridge between the US RLD (PredniSONE from Roxane) and the IR prednisone used in the BE studies (EU-approved Decortin). That is the basis of the bridging to the RLD. Horizon also provided literature to help support the inclusion of toxicology information in the label.*

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO

*If “NO,” proceed to question #5.*

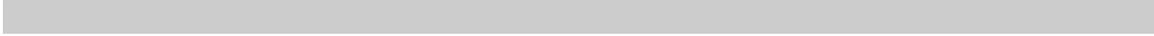
- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If “NO,” proceed to question #5.*

*If “YES”, list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?  
YES  NO



**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
<b>PredniSONE</b>	NDA 17109	Y

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES  NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing: **PredniSONE**

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

***This application provides for a new dosage form (modified-release) tablet.***

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

***(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).***

***Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.***

YES  NO

If "NO" to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?  
YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?  
YES  NO

If “YES” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “NO” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO   
If “NO”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?  
YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?  
*\*(Note: there are multiple pharmaceutical alternatives)*  
YES  NO

If “YES” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “NO” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

**PATENT CERTIFICATION/STATEMENTS**

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed  *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

Drafted by: JordanGarner/6-4-12

505b2 Clearance: Barnes/6-11-12  
Duvall/7-25-12

Finalized: JordanGarner/7-26-12

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MICHELLE Y JORDAN GARNER  
07/27/2012

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 202020 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: RAYOS Established/Proper Name: <i>prednisone (delayed-release)</i> Dosage Form: <i>tablet</i>		Applicant: <i>Horizon Pharma</i> Agent for Applicant (if applicable):
RPM: Michelle Jordan Garner		Division: <i>DPARP</i>
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type:    <input type="checkbox"/> 505(b)(1)    <input checked="" type="checkbox"/> 505(b)(2)                      Efficacy Supplement:    <input type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p><i>NDA 17109 PredniSONE</i></p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>It is a delayed-release; which is different from the RLD's immediate release</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input checked="" type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>	
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>7/26/12</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?                  Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics <sup>3</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority                  Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)                  Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)                  Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input checked="" type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<p><input checked="" type="checkbox"/> None  <input type="checkbox"/> HHS Press Release  <input type="checkbox"/> FDA Talk Paper  <input type="checkbox"/> CDER Q&amp;As  <input type="checkbox"/> Other</p>

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes     No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes     No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes     No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes     No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>4</sup>	7/26/12
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action: Approval 7/26/12
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	7/24/12
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	9/26/11
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	N/A

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	7/24/12
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	9/26/11
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	N/A
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	7/23/12
<ul style="list-style-type: none"> <li>❖ Proprietary Name             <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	3/6/12 Proprietary Name Granted 3/2/12 Review 12/23/11 TCON Memo
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 12/16/11 <input checked="" type="checkbox"/> DMEPA 6/14/12 <input checked="" type="checkbox"/> DRISK 6/15/12 <input checked="" type="checkbox"/> OPDP 6/28/12 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	7/25/12 RPM filing review/memo of filing mtg  <input type="checkbox"/> Not a (b)(2) <input type="checkbox"/> Not a (b)(2) Cleared by b2 cmte 7/25/12
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>6/27/12</u> If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	7/23/12( <i>lbl fax #5</i> ); 7/23/12( <i>lbl fax #4</i> ); 7/19/12( <i>email clarif. to C/C lbl fax</i> ); 7/18/12( <i>carton/ctr lbl fax</i> ); 7/12/12 ( <i>lbl fax #3</i> ) 6/14/12( <i>CMC IR</i> ); 6/14/12( <i>CMC advice</i> ); 6/13/12( <i>lablg fax#2</i> ); 4/27/12( <i>Biopharm IR</i> ); 4/20/12( <i>CMC IR</i> ); 3/29/12( <i>Stats IR</i> ); 3/6/12( <i>Biopharm IR</i> ); 12/23/11 ( <i>Prop. Name W/D Ack Ltr</i> ) 12/15/11( <i>lbl fax #1</i> ) 12/9/11( <i>Filing ltr</i> ) 10/14/11( <i>NDA Ack Ltr</i> )
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> 5/18/12
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> N/A
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> 2/19/10
• EOP2 meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> 12/12/07
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	4/21/06 ( <i>PIND</i> )
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Division Director Summary Review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 7/25/12
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 7/25/12( <i>addendum</i> ); 7/5/12
PMR/PMC Development Templates <i>(indicate total number)</i>	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	12/8/11
• Clinical review(s) <i>(indicate date for each review)</i>	6/21/12
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Page 16; 6/21/12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 6/18/12
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> ( <i>refer to Clin Pharm reviews</i> )
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 6/21/12; 11/18/11
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 6/25/12
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 6/22/12; 11/14/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b>		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> <i>(refer to prod. qly reviews)</i>
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> 7/25/12; 6/22/12; 6/21/12; 6/20/12; 12/1/11; 11/21/11; 10/26/11
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		6/21/12
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup>)</i>		Date completed: 7/20/12 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MICHELLE Y JORDAN GARNER  
07/27/2012



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** June 13, 2012

<b>To:</b> Ingrid Hoos	<b>From:</b> Michelle Jordan Garner
<b>Company:</b> Horizon Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 847-572-1525	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 224-383-3034	<b>Phone number:</b> 301-796-4786

**Subject:** Labeling Comments #4 – NDA 202020 (prednisone)

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**Total no. of pages including  
cover:** 19

---

**Comments:** Courtesy Copy of the Filing Letter

Please acknowledge receipt.

---

**Document to be mailed:**       YES                       NO

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in error, please notify us immediately by telephone at (301) 796-2300.  
Thank you.**

We are currently reviewing your NDA for RAYOS<sup>®</sup>. Submit revised labeling incorporating changes shown in the attached marked up PI. In addition, omit (b) (4)  
[REDACTED].

Submit your response to me via fax at 301-796-9728 or via email at [michelle.jordan@fda.hhs.gov](mailto:michelle.jordan@fda.hhs.gov) by 10a.m. Wednesday July 25, 2012. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact me at 301-796-4786.

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/s/  
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MICHELLE Y JORDAN GARNER  
07/23/2012



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** July 23, 2012

<b>To:</b> Ingrid Hoos	<b>From:</b> Michelle Jordan Garner
<b>Company:</b> Horizon Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 847-572-1525	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 224-383-3034	<b>Phone number:</b> 301-796-4786

**Subject:** Labeling Comments #5 – NDA 202020 (prednisone) –  
**Editorial Edit (Section 14 of label)**

**Total no. of pages including  
cover:** 19

**Comments:**

Please acknowledge receipt.

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**Document to be mailed:**       YES                       NO

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in error, please notify us immediately by telephone at (301) 796-2300.  
Thank you.

We are currently reviewing your NDA for RAYOS<sup>®</sup>. Submit revised labeling incorporating change shown in the attached marked up PI; which may be found in Section 14. In addition, omit (b) (4)

Submit your response to me via fax at 301-796-9728 or via email at [michelle.jordan@fda.hhs.gov](mailto:michelle.jordan@fda.hhs.gov) by 10a.m. Wednesday July 25, 2012. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact me at 301-796-4786.

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MICHELLE Y JORDAN GARNER  
07/23/2012



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: July 18, 2012**

<b>To:</b> Ingrid Hoos	<b>From:</b> Michelle Jordan Garner
<b>Company:</b> Horizon Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 847-572-1525	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 224-383-3034	<b>Phone number:</b> 301-796-4786

**Subject:** NDA 202020 (Rayos) Carton/Container Labeling Comments

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**Total no. of pages including cover:** 4

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**Comments:** Please acknowledge receipt.

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**Document to be mailed:**       YES       NO

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We are currently reviewing your NDA for Rayos. During review of your submitted carton and container labeling, we have identified labeling comments. We request that you re-submit carton and container labeling which addresses these issues.

Submit revised labeling, incorporating changes listed below, via email at [michelle.jordan@fda.hhs.gov](mailto:michelle.jordan@fda.hhs.gov) by **12:00 PM Friday July 20, 2012**. Your response will subsequently need to be submitted officially to the NDA.

The following were identified:

**A. All Trade and Sample Size Container Labels and Carton Labeling (30-count, 100-count)**

1. Ensure the presentation of the established name is at least ½ the size of the proprietary name and has a prominence commensurate with the proprietary name, taking into account all factors, including typography, layout, contrast and other pertinent features as per 21 CFR 201.10(g)(2). Additionally, revise the dosage form to read “Tablets” rather than “Tablet.”
2. Revise the presentation of the proprietary name, RAYOS, from uppercase letters to appear in title case “Rayos” to improve readability of the name.
3. Relocate the net quantity statement (i.e. 30 Tablets) to a location away from the product strength. As currently presented, the net quantity statement appears in close proximity to the product strength; thus, the net quantity may be misinterpreted as strength and vice versa.
4. Relocate or reduce the prominence of the “Rx only” statement because it distracts from important information such as the strength and net quantity statements
5. Remove the graphic design above the proprietary name as it is too close in proximity with proprietary name and distracts from important information such as the proprietary name, established name, and strength presentation.
6. Revise the color block of the 5 mg strength (b)(4) or change the color font used for the proprietary name, and established name (b)(4), so that either the strength or the proprietary and established names appear in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths. The use of the same (b)(4) color font for the proprietary and established names and one of the product’s strengths minimizes the difference between the strengths, which may lead to wrong strength selection errors.

7. Add the statements “Swallow whole” and “Do not crush, divide, or chew tablets” on the side panel of the container labels and carton labeling to prevent wrong technique errors.
8. Add the NDC number to the PDP to appear prominently in the top third of the principal display panel of the label on the immediate container per CFR 207.35(b)(3).
9. Increase the prominence of the strength (i.e. 1 mg) by increasing the font size.

**B. All Trade Size Container Labels (30-count, 100-count)**

Reduce the prominence of the logo graphic located on the side panel of the carton labeling as it distracts from the most important information such as storage information and other relevant information.

**C. Sample Size Container Label (7-count)**

1. See B and revise sample size container labels accordingly.
2. Add the “Rx only” statement on the principle display panel.

**D. All trade size Carton Labeling (30-count and 100-count)**

1. One panel does not contain the proprietary name, established name, and strength. All panels should have the name in case that panel is faced toward the reader.
2. Ensure that the color block at the bottom of the carton labeling is consistent with the color block at the top of the labeling as well as container labels (e.g., 1 mg green and 2 mg orange). Currently, the (b) (4) color block at the bottom of the carton labeling for all three strengths of the products increases the similarity among different strengths.
3. Remove the (b) (4) graphic design on the PDP.

**E. Sample Size Carton Labeling (Professional sample 7-count)**

1. See D1 and revise sample size carton labeling accordingly.
2. Add the “Rx only” statement.

If you have any questions, please contact me at 301-796-4786.

NDA 202020 – Rayos (prednisone)

**Drafted by: MichelleJG 7/18/12**

**Concurrence by: SandyB 7/18/12**

**Finalized by: MichelleJG 7/18/12**

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MICHELLE Y JORDAN GARNER  
07/18/2012



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** July 12, 2012

<b>To:</b> Ingrid Hoos	<b>From:</b> Michelle Jordan Garner
<b>Company:</b> Horizon Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 847-572-1525	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 224-383-3034	<b>Phone number:</b> 301-796-4786

**Subject:** Labeling Comments #3 – NDA 202020 (prednisone)

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**Total no. of pages including cover:** 24

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**Comments:**

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NDA 202020 – RAYOS (prednisone)

We are currently reviewing your NDA for RAYOS<sup>®</sup>. Additional labeling changes may be forthcoming. Submit revised labeling incorporating changes shown in the attached marked up PI.

Submit your response to me via fax at 301-796-9728 or via email at [michelle.jordan@fda.hhs.gov](mailto:michelle.jordan@fda.hhs.gov) by 3pm Tuesday July 17, 2012. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact me at 301-796-4786.

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MICHELLE Y JORDAN GARNER  
07/12/2012



NDA 202-020

**GENERAL ADVICES**

Horizon Pharma, Inc.  
Attention: Ingrid Hoos  
Vice President Regulatory Affairs  
520 Lake Cook Road, Suite 520  
Deerfield, IL 60015

Dear Ms. Hoos:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prednisone Delayed-Release Tablets, 1 mg, 2 mg, and 5 mg. Please also refer to your amendment dated May 4, 2012.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments.

1. The FDA agrees that a paddle speed of 100 rpm is more appropriate for dissolution testing of your drug product. Therefore, a 100 rpm paddle speed is acceptable.
2. The FDA acknowledges your agreement with the Agency's recommended dissolution acceptance criteria of not more than (b) (4) at 3 hours, and  $Q = (b) (4)$  at 7 hours. We agree with your proposal for a lag time acceptance criterion of (b) (4) hours for individual tablets. However, your proposal for Stage 2 and Stage 3 acceptance criteria for the lag time is not acceptable.

Thus, the following dissolution acceptance criteria are recommended for your drug product:

NMT (b) (4) at 3 hours

Mean Lag Time (b) (4) hours. No individual tablet Lag Time should exceed (b) (4) hours

$Q = (b) (4)$  at 7 hours

Please revise the dissolution acceptance criteria accordingly and submit updated specifications for the drug product.

If you have any questions, call Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely yours,

*{See appended electronic signature page}*

Richard T. Lostritto, Ph.D.  
Acting Deputy Director  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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RICHARD T LOSTRITTO  
06/14/2012

## Sharma, Khushboo

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**From:** Sharma, Khushboo  
**Sent:** Thursday, June 14, 2012 3:00 PM  
**To:** 'IHoos@horizonpharma.com'  
**Cc:** Liu, Youbang  
**Subject:** RE: NDA 202020 Information Request

Dear Mr. Hoos

We have another CMC Information request for NDA 202020. Please provide a response by email to Youbang Liu and send an amendment to the submission.

The acceptance criterion of NMT (b) (4) for total impurities in the drug product is not supported by your 24 months stability data. Tighten the acceptance criterion based on your stability data (e.g., (b) (4))

Thank you

*Khushboo Sharma  
Regulatory Health Project Manager  
FDA/CDER/OPS/ONDQA  
Division of New Drug Quality Assessment III  
Phone (301)796-1270*

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/s/  
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KHUSHBOO SHARMA  
06/14/2012



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** June 13, 2012

<b>To:</b> Ingrid Hoos	<b>From:</b> Michelle Jordan Garner
<b>Company:</b> Horizon Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 847-572-1525	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 224-383-3034	<b>Phone number:</b> 301-796-4786

**Subject:** Labeling Comments #2 – NDA 202020 (prednisone)

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**Total no. of pages including cover:** 27

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**Comments:** Courtesy Copy of the Filing Letter  
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We are currently reviewing your NDA for RAYOS<sup>®</sup>. Additional labeling changes may be forthcoming. Submit revised labeling incorporating changes shown in the attached marked up PI. In addition, change the product name from NP01 to RAYOS throughout the PI. Changes have been made to all sections of the PI, to maintain consistency with the labels approved for similar drug products.

Submit your response to me via fax at 301-796-9728 or via email at [michelle.jordan@fda.hhs.gov](mailto:michelle.jordan@fda.hhs.gov) by 3pm Wednesday June 27, 2012. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact me at 301-796-4786.

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MICHELLE Y JORDAN GARNER  
06/13/2012

## Sharma, Khushboo

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**From:** Sharma, Khushboo  
**Sent:** Friday, April 27, 2012 2:22 PM  
**To:** 'lHoos@horizonpharma.com'  
**Cc:** Liu, Youbang  
**Subject:** NDA 202020

Dear Ingrid

We have an Information Request from our Biopharm Review Team regarding NDA 202020. Please provide your response within a week:

1. The data submitted on March 21, 2012 indicate that (b) (4) the paddle speed from 100 rpm (b) (4) does not affect the dissolution profile of your proposed product. Therefore, we recommend revising your proposed dissolution method to reflect a paddle speed of (b) (4)
2. The following dissolution acceptance criteria are recommended for your product:  
**NMT (b) (4) at 3 hours, Lagtime (b) (4) hours for any individual tablet, and Q = (b) (4) at 7 hours.**

This recommendation is based on the mean in-vitro dissolution profiles for all strengths of your proposed product from pivotal clinical batches and primary stability batches at release and under long term (12 months) stability studies. Revise the dissolution acceptance criteria accordingly and submit an updated sheet of specifications for the drug product.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issues under consideration. Otherwise, please provide the appropriate information as an amendment to the submission. In addition, a copy of your response submitted by e-mail (youbang.liu@fda.hhs.gov) will expedite the review of your request. In your cover letter refer to the date on which this information was requested.

*Khushboo Sharma  
Regulatory Health Project Manager  
FDA/CDER/OPS/ONDQA  
Division of New Drug Quality Assessment III  
Phone (301)796-1270*

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KHUSHBOO SHARMA  
04/27/2012



NDA 202-020

**INFORMATION REQUEST**

Horizon Pharma, Inc.  
Attention: Timothy P. Walbert  
Chairman, President and Chief Executive Officer  
1520 Lake Cook Road, Suite 520  
Deerfield, IL 60015

Dear Mr. Walbert:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prednisone Delayed-Release Tablets, 1 mg, 2 mg, and 5 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Approximately fifty nine (59) percent (%) of the reported assay results at release are skewed to the lower side by 2 % or more from the nominal target of 100 % labeled claim. Explain the skewed assay results and provide your corrective approach.
2. We note similar lower than target uniformity of dosage units results (mean of 96%) for all strengths of tablets. Investigate and explain the observed results for uniformity of dosage units at release. Propose corrective actions (e.g., revised manufacturing procedures, analytical methods) to minimize the observed off target results and update the NDA.
3. Your acceptance criterion for (b) (4) in the drug product and actual values are high. Explain why the levels are so high and identify potential contributing sources (b) (4). Provide (b) (4) activity results for your tablets.
4. Your proposal of performing the microbial burden and specified microorganism testing on one out of every ten lots manufactured is not acceptable because it does not comply with 21 CFR 211.165(a) and (b). If you feel you have sufficient data to demonstrate control of drug product bioburden, you may submit the data to justify omission of the finished product microbial limits testing for batch release. Alternately revise the specifications table to perform the testing for each batch. Microbial limits testing should continue to be performed at the initial time point (at a minimum) on stability samples.
5. The manufacturing procedures from Bayer do not specify (b) (4). Specify the (b) (4) to ensure that a consistent (b) (4) is used in each case.

6. Clarify exactly how you will ensure the quality of the excipients by providing details such as, to what extent, and how frequently you will test them before use.
7. Provide representative Certificates of Analysis (CoAs) for all excipients.
8. Provide a representative certificate of compliance to the indirect food additive regulations for each individual component of the container closure system.

If you have any questions, contact Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely,

*{See appended electronic signature page}*

Prasad Peri, Ph.D.  
Branch Chief, Branch VIII  
Division of New Drug Quality Assessment III  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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PRASAD PERI  
04/20/2012



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: March 27, 2012**

<b>To:</b> Ingrid Hoos	<b>From:</b> Michelle Jordan Garner
<b>Company:</b> Horizon Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 847-572-1525	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 224-383-3034	<b>Phone number:</b> 301-796-4786

**Subject:** Information Request – NDA 202020, NP01

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**Total no. of pages including cover:** 3

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**Comments:**

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We are currently reviewing your NDA for NP01, submitted September 26, 2011. We have the following requests for information:

For study protocol NP01-007, the mITT population has a sample size of 231 in the NP01 group and 119 in the Placebo. However, for the analysis of the key secondary endpoint, morning stiffness mITT population has a sample size of LOCF- 216 in the NP01 group, 107 in the placebo group; and BOCF- 215 in the NP01 group, 107 in the placebo group.

1. Explain the discrepancies in sample sizes. With the imputation procedures specified, we would expect that every subject in the mITT population would be included in the analyses.
2. Provide an analysis of the relative change from baseline in Duration of Morning Stiffness for the full mITT population.

Submit your response to me via fax at 301-796-9728 or via email at [michelle.jordan@fda.hhs.gov](mailto:michelle.jordan@fda.hhs.gov), by April 5, 2012. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact me at 301-796-4786.

NDA 202020 – NP01 (prednisone)

Drafted by: MichelleJG 3/26/12

Concurrence by: SandyB 3/26/12

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MICHELLE Y JORDAN GARNER  
03/29/2012



NDA 202020

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Horizon Pharma, Inc.  
520 Lake Cook Road, Suite 520  
Deerfield, Illinois 60015

ATTENTION: Timothy P. Walbert  
Chairman, President, and Chief Executive Officer

Dear Mr. Walbert:

Please refer to your New Drug Application (NDA) dated September 26, 2011, received September 26, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prednisone Tablets, 1 mg, 2 mg, and 5 mg.

We also refer to your December 8, 2011, correspondence, received December 8, 2011, requesting review of your proposed proprietary name, Rayos. We have completed our review of the proposed proprietary name, Rayos, and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your December 8, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Michelle Garner-Jordan, at (301) 796-4786.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
03/06/2012



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: March 6, 2012**

<b>To:</b> Ingrid Hoos	<b>From:</b> Michelle Jordan Garner
<b>Company:</b> Horizon Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 847-572-1525	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 224-383-3034	<b>Phone number:</b> 301-796-4786

**Subject:** Information Request – NDA 202020, NP01

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**Total no. of pages including  
cover: 3**

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**Comments:**

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this communication is not authorized. If you have received this document  
in error, please notify us immediately by telephone at (301) 796-2300.  
Thank you.

We are currently reviewing your NDA for NP01, submitted September 26, 2011. We have the following requests for information:

A paddle speed of 100 rpm being proposed, as part of the dissolution method, is considered (b) (4) and is not recommended. The recommended rotation speeds when using USP Apparatus II are (b) (4)

1. Provide dissolution profiles for the drug product using a paddle speed of (b) (4) as part of the proposed dissolution method.
2. Submit a justification for the most appropriate rotation speed for the proposed dissolution method for the drug product.

Submit your response to me via fax at 301-796-9728 or via email at [michelle.jordan@fda.hhs.gov](mailto:michelle.jordan@fda.hhs.gov), by March 20, 2012. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact me at 301-796-4786.

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/s/  
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MICHELLE Y JORDAN GARNER  
03/06/2012

**MEMORANDUM**

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

**Type of Meeting:** Proprietary Name Review

**Meeting Date:** December 1, 2011; 3:00 – 3:30 PM  
**Meeting Location:** FDA White Oak, Bldg 22, Room 4440, Teleconference

**Application:** NDA 202020  
**Established Name:** Prednisone  
**Applicant:** Horizon Pharma, Inc.

**Meeting Chair:** Carlos M. Mena-Grillasca, Team Leader, DMEPA  
**Meeting Recorder:** Nichelle Rashid

**FDA Attendees:**

Carlos M. Mena-Grillasca, Team Leader, DMEPA, OSE  
Nichelle Rashid, Safety Regulatory Health Project Manager, OSE

**Applicant Attendees:**

Horizon Pharma, Inc.

Amy Grahn, Senior Vice President, Clinical Development and Operations  
Ingrid Hoos, Vice President, Regulatory Affairs  
Jeffrey Sherman, M.D., FACP, Chief Medical Officer, Executive Vice President,  
Development, Manufacturing and Regulatory Affairs  
Todd Smith, Senior Vice President, Marketing and Business Development  
Timothy Walbert, Chairman, President and Chief Executive Officer

Consultants for Horizon Pharma, Inc.

(b) (4)

**Background:**

The Applicant submitted a request for an assessment of the proposed proprietary name, Rayos regarding potential name confusion with other proprietary names in IND 072569 dated February 18, 2011. DMEPA found the proprietary name, Rayos, acceptable from a safety and promotional perspective but recommended the addition of a modifier to reflect the dosage form, delayed extended release. This was communicated to the Applicant via a teleconference call and the Applicant withdrew the application for review of the proposed proprietary name, Rayos, dated August 12, 2011. Subsequently, the Applicant submitted a New Drug Application for NP01 (prednisone, modified release), dated September 29, 2011, and in this submission, they requested for a review of the proposed proprietary name for (b) (4) and the alternate name (b) (4)

DMEPA requested this teleconference to inform Horizon Pharma, Inc. of safety concerns with the primary proposed proprietary name, (b) (4) and to provide recommendations in consideration of the NDA PDUFA goal date of December 25, 2011.

### **Discussion Summary:**

A courtesy call was placed to notify Horizon Pharma, Inc. of DMEPA findings and safety concerns with regards to their proposed name, (b) (4) submitted on September 26, 2011.

First, DMEPA wants to acknowledge that the sponsor previously submitted the proposed proprietary name Rayos to IND 725669. Their request for proprietary name review submitted under the IND indicated that the dosage form was a “modified release tablet”. With the information available at that time, DMEPA recommended that the sponsor include a modifier to the proposed proprietary name to distinguish what DMEPA thought was an extended release formulation from the other formulations on the market.

Subsequently, the sponsor submitted the proposed proprietary name, (b) (4) to NDA 202020. During this review cycle, it is clear to us that the correct dosage form designation for this product is a ‘delayed release tablet’. Given that the product’s release occurs after approximately 3 hours after administration and finishes approximately after 5 hours. Therefore, the modifier (b) (4), intended to convey a (b) (4) formulation is misleading. Thus, DMEPA finds the name unacceptable.

Since DMEPA previously advised the sponsor to include a modifier to the proposed name, under the assumption that the product was an extended-release tablet, DMEPA want to clarify that for a delayed-release formulation DMEPA do not recommend the use of a modifier with the name.

It is the FDA’s policy to review only the primary name submission. However, considering the previous advice that was given DMEPA conducted a preliminary review of their proposed name, Rayos, without a modifier, considering a delayed release formulation. Our preliminary review so far has not identified a safety concern with any other marketed drug product.

### **Regulatory Options:**

- 1- Wait until DMEPA issues a denial letter by the Proposed Proprietary Name PDUFA date of December 25, 2011.
- 2- Withdraw the proprietary name request for (b) (4) and submit Rayos. Although the proprietary name review cycle is 90 days, DMEPA would make their best efforts to complete the review before the 90 days.

## Conclusion

Horizon Pharma, Inc. agreed to withdraw the proposed proprietary name request, (b) (4) and will submit a new request for proprietary name, Rayos. The withdrawal of the proposed proprietary name, (b) (4) was submitted on December 2, 2011.

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/s/  
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NICHELLE E RASHID  
12/23/2011



NDA 202020

**PROPRIETARY NAME REQUEST  
WITHDRAWN**

Horizon Pharma, Inc.  
520 Lake Cook Road  
Suite 520  
Deerfield, IL 60015

ATTENTION: Timothy P. Walbert  
Chairman, President and Chief Executive Officer

Dear Mr. Walbert:

Please refer to your New Drug Application (NDA) dated September 27, 2011, received September 26, 2011, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Prednisone Modified Release Tablets, 1 mg, 2 mg, and 5 mg.

We acknowledge receipt of your December 2, 2011, correspondence, on December 2, 2011, notifying us that you are withdrawing your request for a review of the proposed proprietary name, (b) (4). This proposed proprietary name request is considered withdrawn as of December 2, 2011.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nichelle Rashid, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Michelle Jordan Garner, at (301) 796-4786.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology

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/s/  
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CAROL A HOLQUIST  
12/23/2011



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: December 15, 2011**

<b>To:</b> Ingrid Hoos	<b>From:</b> Michelle Jordan Garner
<b>Company:</b> Horizon Pharma	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 847-572-1525	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 224-383-3034	<b>Phone number:</b> 301-796-4786

**Subject:** Preliminary Labeling Comments – NDA 202020

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**Total no. of pages including cover:** 3

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**Comments: Courtesy Copy of the Filing Letter**

Please acknowledge receipt.

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**Document to be mailed:**       YES       NO

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THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

We are currently reviewing your NDA for NP01. During the preliminary review of your submitted labeling we have identified the following labeling format issues. We request that you resubmit labeling that addresses these issues by 3 PM January 4, 2012. Submit revised labeling, incorporating changes shown below.

Submit your response to me via fax at 301-796-9728 or via email at [michelle.jordan@fda.hhs.gov](mailto:michelle.jordan@fda.hhs.gov). Your response will subsequently need to be submitted officially to the NDA.

The following labeling issues were identified:

**Highlights Section:**

1. Prednisone belongs to an established pharmacologic class. *The following statement is required in the Highlights section of the label: “[ (Drug Product) is a (name of class) indicated for (indication)].”*
2. There should be a white space between each major heading. *Add a space between each section in the Highlights section of the label.*

**Table of Contents:**

3. Avoid using acronyms in subsection headings. *Spell out “NSAIDS”.*

**Full Prescribing Information Section:**

4. Do not number headings within a subsection. *Remove 5.8.1 numbering.*

Submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format, including the aforementioned changes, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

If you have any questions, please contact me at 301-796-4786.

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/s/  
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MICHELLE Y JORDAN GARNER  
12/15/2011



NDA 202020

**FILING COMMUNICATION**

Horizon Pharma, Inc.  
1033 Skokie Boulevard,  
Suite 355  
Northbrook, IL 60062

Attention: Timothy P. Walbert,  
Chairman, President, and CEO

Dear Mr. Walbert:

Please refer to your New Drug Application (NDA) dated September 26, 2011, received September 26, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for NP01 (prednisone) tablet 1 mg, 2 mg, 5 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 26, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 28, 2012.

During our filing review of your application, we identified the following potential review issues:

1. We have concerns regarding the validity of the assessment of morning stiffness and question the clinical relevance of the results. The inclusion of information on morning stiffness in the label will be a review issue.

2. There was no data provided to support the biowaiver for the 1 mg and 2 mg strengths.
3. We are concerned that your delayed release (DR) product may release its entire contents (“dose dumping”) in the stomach when co-administered with alcohol defeating the purpose of the formulation.
4. The graph of stability assay results suggests that at time zero the tablet strength for all lots was below the 100% target. Tablets should be manufactured to target 100%.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

1. To support a biowaiver for the 1 mg and 2 mg strengths, provide *in vitro* comparative dissolution data and f2 similarity values (n=12) in three media: 0.1 N HCl and phosphate buffers pH 4.5 and 6.8, using the same dissolution testing conditions and the 5 mg strength as the reference.
2. Provide a report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the *in vitro* alcohol induced dose dumping study to FDA within six weeks of the expedition date of this letter. Note the following:
  - Dissolution testing should be conducted using the optimal dissolution apparatus and agitation speed in 0.1 N HCl and in the proposed medium. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.
  - The following alcohol concentrations for the *in vitro* dissolution studies are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %.
  - The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first 2 hours.
  - The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference).
3. Provide complete dissolution profile data (raw data and mean values) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for all components of the proposed product.
4. Provide samples of the drug product (core tablets, final coated tablets and the container closure system including the desiccant insert inside the cap).

5. Provide assurance that the drug product release target is 100% for assay for each manufacturer of the drug product.
6. Provide a copy of the related substances test (European Pharmacopoeia) used for the drug substance.
7. Provide representative executed and master batch records for the final drug product filling, sealing and labeling process or provide a description of these processes using an equivalent level of detail as in a batch record.
8. Provide an accurate English translation of the (b) (4) masterbatch record which is provided only in (b) (4)
9. Provide an appropriate Methods Validation package. See the recommendations for methods validation in our draft guidance, "Analytical Procedures and Methods Validation."  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM122858.pdf>)

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult DIVISION NAME. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

(b) (4)

(b) (4)

If you have any questions, call Michelle Jordan Garner, Regulatory Project Manager, at (301) 796-4786.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, MD, PhD  
Director  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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BADRUL A CHOWDHURY  
12/09/2011



NDA 202020

**NDA ACKNOWLEDGMENT**

Horizon Pharma, Inc.  
1033 Skokie Boulevard,  
Suite 355  
Northbrook, IL 60062

Attention: Timothy P. Walbert,  
Chairman, President, and CEO

Dear Mr. Walbert:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Prednisone  
Tablet, 1mg, 2mg, 5mg

Date of Application: September 26, 2011

Date of Receipt: September 26, 2011

Our Reference Number: NDA 202020

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 25, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Pulmonary, Allergy, and Rheumatology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call Michelle Jordan Garner, Senior Regulatory Management Officer, at (301) 796-4786.

Sincerely,

*{See appended electronic signature page}*

Michelle Jordan Garner, MS, OTR/L  
Senior Regulatory Management Officer  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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MICHELLE Y JORDAN GARNER  
10/14/2011



IND 072569

Nitec Pharma  
(c/o) B&H Consulting Services, Inc.  
55 North Gaston Avenue  
Somerville, NJ 08876

Attention: Elizabeth Dupras, RAC  
US Agent, B&H Consulting

Dear Ms. Dupras:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for prednisone modified release tablets.

We also refer to the meeting between representatives of your firm and the FDA on January 26, 2010. The purpose of the meeting was to discuss your planned New Drug Application (NDA).

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2205.

Sincerely,

*{See appended electronic signature page}*

Kathleen Davies, MS  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** January 26, 2010

**TIME:** 12:00 – 1:00 PM (EST)

**LOCATION:** Food and Drug Administration  
White Oak 22, Room 1313  
10993 New Hampshire Ave  
Silver Spring, MD 20993

**APPLICATION:** IND 072569

**PRODUCT:** Prednisone modified release tablets

**INDICATION:** Treatment of Rheumatoid Arthritis (RA)

**SPONSOR:** Nitec Pharma, c/o B&H Consulting Services

**TYPE OF MEETING:** pre-NDA, type B

**MEETING CHAIR:** Jeff Siegel, MD, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

**MEETING RECORDER:** Kathleen Davies, MS, Regulatory Health Project Manager

<b>FDA Attendees</b>	<b>Title</b>
Bob A. Rappaport, MD	Director, Division of Anesthesia, Analgesia and Rheumatology Products
Rigoberto Roca, MD	Deputy Director
Jeff Siegel, MD	Clinical Team Leader
Deborah Seibel, MD	Clinical Reviewer
Prasad Peri, PhD	Acting Branch Chief, Office of New Drug Quality Assessment
Dan Mellon, PhD	Pharmacology Toxicology Supervisor
Asoke Mukherjee, PhD	Pharmacology Toxicology Reviewer
Dionne Price, PhD	Statistical Team Leader
David Petullo, MS	Statistical Reviewer
Suresh Doddapaneni, PhD	Clinical Pharmacology Team Leader
Zhihong Li, PhD	Clinical Pharmacology Reviewer
Kathleen Davies, MS	Regulatory Health Project Manager
<b>Nitec</b>	<b>Title</b>

Hans Rensland, PhD	Vice President, Regulatory Affairs
Achim Schaffler, PhD	Executive Vice President, Research and Development
Markus Vogt, PhD	Vice President, Global Quality and Compliance
Stephan Witte, PhD	Chief Medical Officer
Elizabeth Dupras, RAC	Senior Project Manager, B&H Consulting Services Inc.
Helen Ribbans, RAC	President, B&H Consulting Services Inc.
(b) (4)	Consultant to NITEC
(b) (4)	Consultant to NITEC

## **BACKGROUND**

Nitec submitted a pre-NDA meeting request for guidance regarding their planned 505(b)(2) application for the treatment of RA.

Each of the Sponsor's questions is presented below in italics, followed by the Division's response in bold. A record of the discussion that occurred during the meeting is presented in normal font. The Division provided written responses to the firm on January 22, 2010.

## **REGULATORY**

*Question 1. Does the Agency agree with the proposed eCTD submission of the planned 505(b)(2) application?*

### **FDA Response:**

**You propose an eCTD submission of your planned 505(b)(2) application. This appears acceptable. Refer to <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm> for additional information on eCTD submissions.**

Discussion:

There was no further discussion on this point.

*Question 2. Does the Agency agree that the proposed 505(b)(2) application meets the requirements for this approach to the ISE?*

### **FDA Response:**

**You propose to include the ISE in Module 2 only of your eCTD submission. However, as outlined in the [Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document](#), the ISE should be in Module 5.**

**Specifically, the Guidance states,**

**In general, Module 5, specifically section 5.3.5.3, Reports of Analyses of Data from More than One Study (Including Any Formal Integrated Analyses, Meta-Analyses, and Bridging Analyses), is the appropriate location for the ISE and ISS. This module is designed to contain more detailed in-depth analyses, and unlike Module 2, Module 5 has no space limitation. Module 5 is the appropriate CTD section for analyses containing large appendices of tables, figures, and datasets typically found in an ISE and ISS. In general, Module 5, specifically section 5.3.5.3, Reports of Analyses of Data from More than One Study (Including Any Formal Integrated Analyses, Meta-Analyses, and Bridging Analyses), is the appropriate location for the ISE and ISS. This module is designed to contain more detailed in-depth analyses, and unlike Module 2, Module 5 has no space limitation. Module 5 is the appropriate CTD section for analyses containing large appendices of tables, figures, and datasets typically found in an ISE and ISS.**

Discussion:

There was no further discussion on this point.

*Question 3. Does the Agency agree that the proposed 505(b)(2) application meets the requirements for this approach to the ISS?*

**FDA Response:**

**See Response to Question #2.**

Discussion:

There was no further discussion on this point.

*Question 4. Does the Agency agree with the electronic datasets NITEC intends to include in the NDA?*

**FDA Response:**

**The Division agrees with this approach; however, upon review, there may be additional requests for information.**

Discussion:

There was no further discussion on this point.

*Question 5. NITEC proposes to submit CRFs only for those subjects who died on study or discontinued due to AEs, plus CRFs for those subjects who had serious adverse events (SAEs). All other CRFs will be available upon request. Does the Agency agree with this proposal?*

**FDA Response:**

**The Division agrees with this approach.**

Discussion:

There was no further discussion on this point.

*Question 6. Does the Agency agree with [REDACTED] pediatric patients?* (b) (4)

**FDA Response:**

[REDACTED] (b) (4)

Discussion:

There was no further discussion on this point.

## **NONCLINICAL**

*Question 7. Does the Agency concur that no additional clinical and nonclinical assessments are necessary for 505(b)(2) NDA?*

**FDA Response:**

**The Division agrees that no additional nonclinical toxicology studies for prednisone will be required to support the filing of the NDA for your drug product.**

**Final determination of the adequacy of the nonclinical portions of the NDA to support product approval can only be determined upon review of the submitted materials.**

Discussion:

There was no further discussion on this point.

*Question 8. Does the Agency agree that this data is sufficient to support the planned 505(b)(2) application?*

**FDA Response:**

**See additional nonclinical comments.**

Discussion:

There was no further discussion on this point.

## **CLINICAL**

*Question 9. Does the Agency agree that the ACR20 results of the CAPRA-2 (NP01-007) study support a label of: "...reducing signs and symptoms..." in the planned 505(b)(2) application?*

**FDA Response:**

**Since your product is a modified preparation of prednisone, an approved medication, positive results of your CAPRA-2 study would support a label claim of "...reducing signs and symptoms..." of rheumatoid arthritis.**

**For this confirmatory study, the primary analysis should be conducted using the treatment patients were randomized to rather than the treatment they received. As a supportive analysis, you should repeat the analysis using the treatment patients actually received. This comment was previously conveyed in a letter dated August 25, 2009.**

Discussion:

The Sponsor requested clarification for the proposed indication statement as to why the statement would be unacceptable as, (b) (4)

The Division explained that the general policy as an Agency is to shift from lengthy indication statements, which include labeling claims, to a simplified general indication statement, and moving any labeling claims to the clinical studies section of the full prescribing information (FPI). This

allows for a clinician to more easily determine the use of the drug, and then can look to other sections of the FPI to determine what specific benefits have been demonstrated. The Sponsor can still promote any claims listed in the clinical studies section of the label. The Division directed the Sponsor to recently approved products for rheumatoid arthritis as examples of the current format for indications and clinical studies sections.

*Question 10. Does the Agency agree that the reduction of morning stiffness can be included in the label claim for prednisone, as demonstrated by the results of adequate and well controlled replicate clinical studies (CAPRA-1 and CAPRA-2)?*

*If the Agency does not agree that the reduction of morning stiffness can be included in the label claim for prednisone, does the Agency agree that the data can be reported in the Clinical Studies section of the labeling?*

**FDA Response:**

**In principle, positive results from your CAPRA-1 and CAPRA-2 studies could support a labeling claim of improvement in morning stiffness. However, the indication would be limited to, “treatment of Rheumatoid Arthritis.” If review of the data supports the label claim of reduction of morning stiffness, the clinical findings would likely be described in the Clinical Studies section and not in the Indication section. Since improvement in morning stiffness is a Patient Reported Outcome, you should consult the PRO guidance document and include with your submission documentation of appropriate validation of this labeling claim and justification of the instrument used to measure morning stiffness in support of your claim.**

**Your LOCF imputation strategy for patients that discontinued early is not appropriate. You may be imputing a good score for a patient that was not able to tolerate study drug. You should use baseline observation carried forward for these patients in the primary analysis, i.e., there would be no improvement in the baseline score. You may explore other imputation strategies as part of your sensitivity analyses.**

Discussion:

See Discussion under Question #9.

*Question 11. Does the Agency agree that these exposure data are adequate to support the approval of a 505(b)(2) NDA registration package for prednisone?*

**FDA Response:**

**In principle, the data you propose would provide adequate exposure data for your new formulation. If on review of the complete safety data new signals are identified, then additional safety data may be required.**

**Although prednisone is approved for use in rheumatoid arthritis, there is increasing medical awareness of the risks associated with long-term corticosteroid exposure. Of note, the ACR guidelines on DMARD treatment of RA did not include corticosteroids. Therefore review of your NDA submission may include a presentation to the Arthritis Advisory Committee to solicit their advice and comments.**

Discussion:  
There was no further discussion on this point.

## **CHEMISTRY, MANUFACTURING AND CONTROLS**

*Question 12. Does the Agency agree to NITEC's proposal to include executed batch records in a matrix design?*

**FDA Response:**

**This proposal is acceptable; however, additional information may be requested during the NDA review regarding details of the manufacturing process and controls.**

**We remind you that executed batch records must be submitted in English.**

Discussion:  
There was no further discussion on this point.

*Question 13. Does the Agency agree that the Qualification Plan is adequate to support Bayer as an additional manufacturing site for the bulk drug product in the initial NDA?*

**FDA Response:**

**Your proposal to qualify Bayer as a commercial drug product manufacturer by a qualification protocol in the NDA is reasonable. In addition to a detailed comparability protocol, provide site-specific stability data from Bayer, i.e., 3-months long-term and accelerated storage, for at least on one batch per strength.**

**Also, clarify if Bayer is intended to be the sole commercial manufacturing site.**

Discussion:  
There was no further discussion on this point.

*Question 14. In support of a proposed expiry date, will the Agency accept the 24-month long-term stability data from (b) (4) at the time of NDA filing along with 3-month stability data from Bayer supplemented by 6-month data prior to month 5 of review?*

**FDA Response:**

**Provide the longest available stability data from Bayer at the time of the NDA submission. While every effort will be made to review any stability amendments to the NDA, their review will depend on the timeliness of submission, extent of submitted data, and available resources.**

Discussion:  
There was no further discussion on this point.

*Question 15. Does the Agency agree to the specification concept of two time-points to adequately control the drug release characteristics of prednisone? Does the Agency agree to the dissolution levels of (b) (4) at the proposed times of 3.0 and 7.0 hours, respectively?*

**FDA Response:**

**You have not provided sufficient information to evaluate the adequacy of this proposal.**

**Provide the full dissolution method report for review to determine the adequacy of your proposed dissolution specifications. Once this data is submitted within the NDA and the totality of the data is reviewed a recommendation on the dissolution method and specifications will be made.**

Discussion:

There was no further discussion on this point.

*Question 16. Does the Agency agree to the specification settings for chemical purity?*

**FDA Response:**

**We do not agree. You must establish specifications for impurities and degradants in the drug substance and product, based on ICH Q3A(R) and Q3B(R) Guidelines. We note that process capability may allow for tightened limits.**

**Refer to the nonclinical comments regarding qualification of impurities and degradants and structural alerts.**

Discussion:

The Sponsor requested clarification as to why ICH Q3A and Q3B Guidelines would be insufficient for chemical purity of their product. The Division clarified that these Guidelines are appropriate for impurities and degradants that are not structural alerts; however, any structural alerts identified in their product would be subject to a higher level of scrutiny than ICH Guidelines. For example, genotoxic impurities have different specifications that are more stringent than ICH Guidelines, as outlined in the FDA Draft Guidance for Industry from December 2008 titled "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches" which can be found on the FDA website at the following location:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079235.pdf>. Final determination of the purity specifications for any impurity and degradant in the product will be a review issue.

**ADDITIONAL COMMENTS**

**CHEMISTRY, MANUFACTURING AND CONTROLS**

**Provide a list of all manufacturing and testing facilities, in alphabetical order, with a statement about their cGMP status and whether they are ready for inspections at the time of NDA submission. For all manufacturing sites, provide a contact name, telephone number, facsimile number, and email address. Clearly specify the responsibilities of each facility, and which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk approvability of the NDA.**

Discussion:

There was no further discussion on this point.

**NONCLINICAL**

1. Clarify if you still intend to refer to the Agency's previous findings of safety and efficacy of ANDA 80-356 (Watson Labs 5 mg tablet) to support your 505(b)(2) application.
2. We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf>)).
3. If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.
4. Your NDA submission should include a detailed discussion of the nonclinical information in the published literature and should specifically address how the information within the published domain impacts the safety assessment of your drug product. This discussion should be included in module 2 of the submission. Copies of all referenced citations should be included in the NDA submission in module 4. Journal articles that are not in English must be translated into English. The nonclinical information in your drug product labeling must include relevant exposure margins with adequate justification for how these margins were obtained. As you intend to rely upon the Agency's previous finding of safety for an approved product, you must consider the potential need for additional pharmacokinetic data to bridge your product to the referenced product labeling.
5. We acknowledge that you intend to follow ICHQ3B(R) qualification thresholds for the drug product. For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per (ICHQ3A(R), ICHQ3B(R)). Adequate qualification must include:
  - i. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.



**ACTION ITEMS:**

1. The Sponsor acknowledges that the indication for their product will be a general claim for treatment of rheumatoid arthritis and any additional claims would be outlined in the clinical trials section of their full prescribing information (FPI).
2. The Sponsor acknowledges that any structure alerts in their product may be required to have different specifications than general ICH guidelines for impurities and degradants and that final determination of specification of their product will be a review issue.
3. The Sponsor confirmed their intended referenced product is the Roxane product and acknowledges that their label must be submitted in Physician Labeling Rule (PLR) format. The Sponsor will specifically designate by number with ANDA(s) they intend to reference.

## Attachment 1

### General CLINICAL Comments

The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the manual of policies and procedures (MAPP) 6010.3 at: <http://www.fda.gov/cder/mapp/6010.3.pdf>.

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. Section 2.6 Other Relevant Background Information - important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 5.3 Exposure-Response Relationships - important exposure-response assessments.
3. Section 7.1.6 - Less common adverse events (between 0.1% and 1%).
4. Section 7.1.7.3.1 - Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
5. Section 7.1.7.3.2 - Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
6. Section 7.1.7.3.3 - Marked outliers and dropouts for laboratory abnormalities.
7. Section 7.1.8.3.1 - Analysis of vital signs focused on measures of central tendencies.
8. Section 7.1.8.3.2 - Analysis of vital signs focused on outliers or shifts from normal to abnormal.
9. Section 7.1.8.3.3 - Marked outliers for vital signs and dropouts for vital sign abnormalities.
10. Section 7.1.9.1 – Overview of ECG testing in the development program, including a brief review of the nonclinical results.
11. Section 7.1.9.3. – Standard analyses and explorations of ECG data.
12. Section 7.1.16 – Overdose experience.
13. Section 7.4.2.1 - Explorations for dose dependency for adverse findings.
14. Section 7.4.2.2 - Explorations for time dependency for adverse findings.
15. Section 7.4.2.3 - Explorations for drug-demographic interactions.
16. Section 7.4.2.4 - Explorations for drug-disease interactions.
17. Section 7.4.2.5 - Explorations for drug-drug interactions.
18. Section 8.2 - Dosing considerations for important drug-drug interactions.
19. Section 8.3 - Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

### Sites for Inspection

To assist the clinical reviewer in selecting sites for inspection, include a table in the original NDA for each of the completed Phase 3 clinical trials that has the following columns:

1. Site number
2. Principle investigator
3. Location: City State, Country
4. Number of subjects screened
5. Number of subjects randomized
6. Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites)
7. Number of protocol violations (Major, minor, definition)

### Common PLR Labeling Deficiencies

#### Highlights:

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3. The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4. The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).
6. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].

7. **The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:**

**“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”**

8. **Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.**
9. **Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).**
10. **A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]**
11. **Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]**
12. **The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]**
13. **A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.**
14. **A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]**

**Contents (Table of Contents):**

15. **The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]**
16. **The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]**
17. **Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.**
18. **Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.**

19. When a subsection is omitted, the numbering does not change.
20. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

- 8.1 Pregnancy
- 8.3 Nursing Mothers (not 8.2)
- 8.4 Pediatric Use (not 8.3)
- 8.5 Geriatric Use (not 8.4)

21. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents:

“\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

**Full Prescribing Information (FPI):**

22. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
23. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
24. Do not refer to adverse reactions as “adverse events.” Refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/cder/guidance>.
25. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [*see Use in Specific Populations (8.4)*] not See *Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]
26. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
27. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]

28. **The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.**
29. **There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.**
30. **The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.**
31. **Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.**
32. **If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.**
33. **Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.**
34. **Refer to the Institute of Safe Medication Practices’ website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for a list of error-prone abbreviations, symbols, and dose designations.**

**CDISC Data Requests to Sponsors  
Quantitative Safety and Pharmacoepidemiology Group**

**Safety Analysis Plan**

**In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, include a Quantitative Safety Analysis Plan (QSAP). The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis ([www.cdisc.org](http://www.cdisc.org)).**

**At a minimum the Safety Analysis Plan should address the following components:**

- a. **Study design considerations (See: *FDA Guidance to Industry: Pre-Marketing Risk Assessment*, <http://www.fda.gov/CDER/guidance/6357fnl.pdf>).**
- b. **Safety endpoints for Adverse Events of Special Interest (AESI)**
- c. **Definition of Treatment Emergent Adverse Event (TEAE)**
- d. **Expert adjudication process (Expert Clinical Committee Charter)**
- e. **Data/Safety Monitoring Committee (DSMC): (Submit charter for FDA review) by**
- f. **Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.**
- g. **When unanticipated safety issues are identified the Quantitative Safety Analysis Plan may be amended. Amendments should be filed in accordance with FDA regulations.**

### **Study Data Tabulation Model (SDTM) Issues**

1. **The current published SDTM and SDTM Implementation Guide (SDTMIG) carefully should be followed. Refer to the SDTMIG section on Conformance (3.2.3)**
2. **Domains**
  - a. **There are additional domains listed below that are not included in the current SDTMIG. Information on these domains may be obtained at [www.CDISC.org](http://www.CDISC.org) and are expected to be published in the next versions of SDTM and SDTMIG (Version 3.1.2). If applicable, use these domains.**
    - **(DV) Protocol deviations**
    - **(DA) Drug Accountability**
    - **(PC, PP) Pharmacokinetics**
    - **(MB, MS) Microbiology**
    - **(CF) Clinical Findings**
  - b. **The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains.**
    - **Tumor information**
    - **Imaging Data**
    - **Complex Inclusion/Exclusion Criteria**
3. **Variables**
  - a. **All required variables are to be included.**
  - b. **All expected variables must be included in all SDTM datasets.**

- c. **Variables (expected or permissible) for which no values will be submitted must be explicitly stated and discussed with the review division.**
  - d. **A list of all Permissible variables that will be included and those that will not be included for each domain must be provided for review and discussed with the review division.**
  - e. **A list and description of all variables that will be included in the Supplemental Qualifier dataset must be provided.**
  - f. **Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.**
4. **Specific issues of note:**
- a. **SDTM formatted datasets must not provide replication of core variables (such as treatment arm) across all datasets.**
  - b. **Only MedDRA preferred term and system organ class variables are allowed in the AE domain. However, the other levels of the MedDRA hierarchy may be placed in the SUPPQUAL dataset or an ADaM dataset.**
  - c. **These issues can be addressed through the request for ADaM datasets**

#### **Analysis Data Model (ADaM) Issues**

1. **Specify which ADaM datasets you intend to submit.**
2. **Include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.**
3. **Discuss the structure of the datasets with the reviewing division and specify in the QSAP.**
4. **Within each adverse event analysis dataset, include all levels of the MedDRA hierarchy as well as verbatim term.**
5. **Indicate which core variables will be replicated across the different datasets, if any.**
6. **SDTM and ADaM datasets must use the unique subject ID (USUBJID). Each unique subject identifier must be retained across the entire submission.**

#### **General Items**

##### **Controlled terminology issues**

- a. **Use a single version of MedDRA for a submission. Does not have to be most recent version**

- b. We recommend that the WHO drug dictionary be used for concomitant medications.**
- c. Refer to the CDISC terminology for lab test names.**
- d. Issues regarding ranges for laboratory measurements must be addressed.**

### **Integrated Summary of Effectiveness**

**Please refer to the Guidance for Industry located at the following web page**

**<http://www.fda.gov/cder/guidance/7694dft.pdf>**

**Please refer to Guidance for Industry - Integrated Summaries of Effectiveness and Safety:  
Location Within the Common Technical Document**

**<http://www.fda.gov/CDER/GUIDANCE/8524fnl.pdf>**

### **Dataset Comments**

**The Division requests the following for the submitted datasets:**

- 1. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.**

**The integrated safety dataset that must include the following fields/variables:**

- a. A unique patient identifier**
- b. Study/protocol number**
- c. Patient's treatment assignment**
- d. Demographic characteristics, including gender, chronological age (not date of birth), and race**
- e. Dosing at time of adverse event**
- f. Dosing prior to event (if different)**
- g. Duration of event (or start and stop dates)**
- h. Days on study drug at time of event**
- i. Outcome of event (e.g. ongoing, resolved, led to discontinuation)**
- j. Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).**

**k. Marker for serious adverse events**

**l. Verbatim term**

- 2. The adverse event dataset must include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset must also include the Verbatim term taken from the case report form.**
- 3. See the attached mock adverse event data set that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables must appear and does not address other content that is usually contained in the adverse event data set.**
- 4. In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.**
- 5. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.**
- 6. Provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.**
- 7. Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.**
- 8. The spelling and capitalization of MedDRA terms must match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.**
- 9. Also, for the concomitant medication dataset, you must use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.**

- 10. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result must be in numeric format.**
- 11. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.**
- 12. In every dataset, all dates must be formatted as ISO date format.**
- 13. Across all datasets, the same coding must be used for common variables, e.g. "PBO" for the placebo group. Datasets must not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable must be included in the datasets.**
- 14. All datasets must contain the following variables/fields (in the same format and coding):**
  - a. Each subject must have one unique ID across the entire NDA**
  - b. Study number**
  - c. Treatment assignment**
  - d. Demographic characteristics (age, race, gender, etc.)**
- 15. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities must be provided. Also, a listing must be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values must include assessments of changes from baseline to worst value, not simply the last value.**
- 16. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.**
- 17. For patients listed as discontinued to due "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.**
- 18. With reference to the table on the following page, note that the HLG T and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLG T terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data.**

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

## Quality Assessment for NDA/BLA Submissions (May 2009 version)

**Purpose:** This assessment is intended to be used by both the applicant and members of CDER's review team. It is designed to guide them through the pertinent sections of an application and to assist in assessing the content of the NDA/BLA submission as well as the overall review process. It is to be used to record information solely to facilitate discussion of lessons learned at the post-action feedback meeting of both parties. It is to play no role in the FDA action taken on an application and is not to be used in dispute resolution. It will not be archived with the application by FDA.

**When to Use:** At this time, CDER will offer this assessment and the post-action feedback meeting for all NMEs and original BLAs; CDER may offer these for other applications and supplements. Both the applicant and review team members are encouraged to periodically add information to their Quality Assessment form during the review process. This assessment should be used to guide post-action feedback meetings between the FDA and the application.

### **Instructions for Completing the Quality Assessment**

**Applicant:** This assessment should be filled out both while preparing the submission and during the review cycle. You can use it to record your experience with the review process, including the steps preceding submission of the BLA/NDA.

**The Post-Action Feedback Meeting:** This assessment will be used in the post-action feedback meeting only as a guide for the discussion. The applicant and all CDER reviewers should bring their completed assessment and use it as a reference for issues that are pertinent to the discussion. Due to the sizable content of the assessment, it is not expected that every question be discussed. The meeting should focus on those items that provide lessons learned (i.e., things that worked well and things that did not) for future applications.

**Collection and Archiving:** This assessment is not to be collected and it is not to be archived. It is for the applicant and each CDER reviewer to retain and dispose of at their discretion.

\_\_\_ Applicant Assessment    Applicant: \_\_\_\_\_  
 \_\_\_ FDA Assessment            OND Division: \_\_\_\_\_  
 (cycles)

NDA# \_\_\_\_\_ BLA# \_\_\_\_\_  
 Action on Application: \_\_\_\_\_ (after \_\_\_ review  
 Number of amendments: \_\_\_\_\_ (including \_\_\_ major amendments)

Review Phase	Activity	Provide comments or specific examples to characterize application quality and facilitate discussion (e.g., if you don't think communication was timely, describe the frequency versus your expectation).
Pre- and Peri-Submission Activities	<b>A Target Product Profile (TPP) was used during drug development that improved the review process by aligning sponsor goals with proposed label claims during the IND process.</b> <a href="http://www.fda.gov/cder/guidance/6910dft.htm">http://www.fda.gov/cder/guidance/6910dft.htm</a>	
	<b>Special Protocol Assessments were utilized and benefited the application.</b>	
	<b>The pre-NDA/BLA meeting included discussion of all topics important for preparation of a complete, high quality application.</b>	
	<b>(If electronic submission) A pre-NDA/BLA application format discussion, held with FDA in advance of submission, facilitated development of a higher quality application.</b>	
	<b>The FDA indicated prior to submission that test results appeared to meet pre-specified endpoints and should be submitted for review.</b>	
	<b>An (optional) orientation session was held (within 21 days of submission) to permit applicant to familiarize reviewers with the content and navigation of the submission; this resulted in a more efficient FDA review.</b>	
	<b>Leading up to submission, interactions between FDA and the applicant throughout the drug development process were optimal for developing a high quality application.</b>	

Review Phase	Activity	Provide comments or specific examples to characterize application quality and facilitate discussion (e.g., if you don't think communication was timely, describe the frequency versus your expectation).
<b>Overall Application Format and Content</b>	<b>The presentation and construction of the application followed the required format and was indexed appropriately.</b>	
	<b>(If electronic submission) The electronic submission loaded without difficulty.</b>	
	<b>(If electronic submission) Proper eCTD lifecycle XML relationships were established in all submissions.</b>	
	<b>(If electronic submission) All hyperlinks in the application worked appropriately.</b>	
	<b>The application included:</b> <ul style="list-style-type: none"> <li>• <b>Required forms appropriately completed</b></li> <li>• <b>Information requested by FDA during pre-submission drug development and per applicable guidance and regulations</b></li> </ul>	
	<b>The application appropriately reflected previous advice and requests from FDA (e.g., regarding development program, study design and endpoints, GCP issues and analysis of results, CMC issues) or included reasonable justification for all deviations from FDA guidance or pre-submission advice.</b>	
<b>Summaries/ Overviews</b>	<b>The summaries highlighted the important issues.</b>	
	<b>The summaries accurately reflected supporting data, including appropriate links.</b>	
<b>Technical Sections</b>	<b>Datasets were complete and in a format to facilitate FDA analysis.</b>	
	<b>Appropriate analyses were performed by the applicant to evaluate efficacy, safety, and product quality, e.g., claims were based on pre-specified endpoints and analyses; any deviations justified; conformed to ICH and other guidelines.</b>	

Review Phase	Activity	Provide comments or specific examples to characterize application quality and facilitate discussion (e.g., if you don't think communication was timely, describe the frequency versus your expectation).
Site Inspections	Facilities were available for inspection upon application submission.	
	Facility inspections were completed in a timely manner.	
	Clinical site inspections were completed in a timely manner.	
	All deviations from GCP were identified for each clinical site in the initial submission and impact of deviations were discussed in the application.	
Post-marketing Requirements (PMR) and Commitments (PMC)	PMRs and PMCs, with timelines, conforming to ICH guidelines were included in the initial submission. Examples include PREA studies, confirmatory studies for accelerated approval, studies to evaluate previously identified safety issues.	
	If the need for PMRs or PMCs was identified by FDA during application review, discussion of postmarketing study proposals and timelines followed GRMP timelines.	
Risk Evaluation and Mitigation Strategy (REMS)	REMS, as discussed during pre-submission meeting, were included in the initial submission.	
	If a need for REMS was identified by FDA during application review, request for/discussion of REMS followed GRMP timelines.	
	FDA provided rationale for modifications to applicant's REMS.	
	Applicant followed FDA Guidance regarding content/organization of REMS.	
Labeling	Labeling contained annotations and/or hyperlinks to the location of supporting data in the application.	
	All references in proposed labeling were included in the submission.	

Review Phase	Activity	Provide comments or specific examples to characterize application quality and facilitate discussion (e.g., if you don't think communication was timely, describe the frequency versus your expectation).
	<p><b>Applicant followed FDA Guidance regarding content/organization of labeling, including patient labeling or Medication Guide and carton/container labeling.</b></p>	
	<p><b>FDA provided rationale for substantive modifications to applicant's labeling and FDA proposed changes were consistent with Guidances/policy.</b></p>	
	<p><b>FDA and applicant followed GRMP timelines for labeling discussions.</b></p>	
	<p><b>Applicant's submission of proprietary name review request followed FDA guidance (e.g., more than on proposed name). If submitted during the IND review, did this "add value" to proprietary name review? If not, why not?</b></p>	
<b>Communi- cation</b>	<p><b>FDA requests for information were clearly stated and reflected understanding of application contents.</b></p>	
	<p><b>The applicant responded to information requests raised during the review in a <i>timely</i> manner, including:</b></p> <ul style="list-style-type: none"> <li>• <b>Information requests during first 60 days</b></li> <li>• <b>Day-74 letter</b></li> <li>• <b>Information requests after 60 days</b></li> <li>• <b>Discipline Review letters</b></li> </ul>	
	<p><b>Applicant responded to issues raised during the review in a <i>complete</i> manner, i.e., no follow-up was required.</b></p>	
	<p><b>Did application contain information requested during IND review? Were there deficiencies communicated by FDA during the review (e.g., day 74, etc.) that should have been anticipated based on FDA comments prior to submission of the application?</b></p>	

Review Phase	Activity	Provide comments or specific examples to characterize application quality and facilitate discussion (e.g., if you don't think communication was timely, describe the frequency versus your expectation).
	Could issues raised by FDA during application review have been identified by FDA or applicant prior to submission?	
	How might communication or discussion of information requests been more efficient?	
	Significant deviations from the milestone timeline by FDA were communicated to the applicant.	

**Additional comments from any disciplines or consultant reviewers:**

**Overall Assessment:**

- **Identify three critical factors that contributed to the application's outcome.**
  - 1.
  - 2.
  - 3.
- **In retrospect, would a refusal-to-file decision have better utilized resources and expedited time to approval?**
- **Provide any comments on how to improve the process.**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-72569	GI-1	NITEC PHARMA	Lodotra (Prednisone) Modified Release Tablet

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

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/s/

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KATHLEEN M DAVIES  
02/19/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

PIND 72,569

James M. Audibert  
c/o Nitec Pharma AG  
30 Dale Drive  
Summit, NJ 07901

Attention: James M. Audibert  
U.S. Representative for Nitec Pharma AG

Dear Mr. Audibert:

Please refer to your Pre-Investigational New Drug Application (PIND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LODOTRA™ (prednisone modified release) Tablet.

We also refer to the meeting between representatives of your firm and the FDA on March 24, 2006. The purpose of the meeting was to discuss the development plan (three PK/PD studies and one efficacy trial) and obtain guidance for on submitting a 505(b)(2) application.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796 1173.

Sincerely,

*{See appended electronic signature page}*

Paul Z. Balcer  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

## MEMORANDUM OF TELECONFERENCE

**MEETING DATE:** Friday, March 24, 2006

**TIME:** 10:00 - 11:00 a.m. (EST)

**LOCATION:** Teleconference from White Oak, Conference Rm #3270,  
10903 New Hampshire Ave, Silver Spring, MD 20993-0002

**APPLICATION (DRUG):** PIND 72,569 LODOTRA™ (prednisone modified release) Tablet

**INDICATION:** Treatment of Rheumatoid Arthritis

**SPONSOR:** Nitec Pharma AG

**TYPE OF MEETING:** Type C, pre-IND, Guidance

**MEETING CHAIR:** Bob A. Rappaport, M.D.

**MEETING RECORDER:** Paul Z. Balcer, RHPM

**MEETING OBJECTIVE:** Discussion of development plan (three PK/PD studies and one efficacy trial) and obtain guidance for on submitting a 505(b)(2) application.

**BACKGROUND:**

**Meeting request:** January 12, 2006, received January 18, 2006

**Meeting package:** February 17, 2006 received February 22, 2006

A type B meeting was granted on February 6, 2006.

### FDA Attendees

Name	Title
Bob Rappaport, M.D.	Director, Division of Anesthesia, Analgesia and Rheumatology Products
Rigoberto Roca, M.D.	Deputy Director (Rheumatology Team)
Joel Schiffenbauer, M.D.	Clinical Team Leader (Rheumatology)
Carolyn L. Yancey, M.D.	Clinical Reviewer
Yongman Kim, Ph.D.	Statistics Reviewer
Suresh Doddapaneni, Ph.D.	Clinical Pharmacology Team Leader
David Lee, Ph.D.	Clinical Pharmacology Reviewer
Ali Al Hakim, Ph.D.	Chemistry Reviewer
Dan Mellon, Ph.D.	Pharmacology/Toxicology Team Supervisor
Paul Z. Balcer	Regulatory Health Project Manager

**Nitec Pharma AG/Consultant Attendees**

<b>Name</b>	<b>Title</b>
Achim Schaeffler, Ph.D.	Co-founder of Nitec Pharma, Head of Research and Development
James Audibert	VP Strategic Marketing, U.S. Representative
Joachim Riotte, Ph.D.	Regulatory Affairs
(b) (4)	Clinical Consultant
(b) (4)	Consultant, PK/PD modeling, (b) (4)

**AGENDA QUESTIONS from SPONSOR and FDA COMMENTS:**

**The Sponsor's questions and the FDA responses are in normal font. Any additional discussion is in bold font. The FDA responses were provided to the Sponsor on March 23, 2006.**

1. Does the Agency agree that the development plan qualifies the NDA of LODOTRA™ as an application corresponding with section 505(b)(2) of the Act?

FDA Response

Yes, the proposed development plan for prednisone modified-release tablet (LODOTRA) is acceptable under the 505(b)(2) route.

However, your product formulation containing (b) (4) of (b) (4) exceeds the levels in previously approved products (b) (4). Therefore, your IND should provide safety qualification for this level of exposure to (b) (4). Please refer to the guidance document: *Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005)*, available at <http://www.fda.gov/cder/guidance/guidance.htm>, specifically to the following paragraph:

“the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently *proposed level of exposure, duration of exposure, or route of administration*” [emphasis added].

Additionally, the following comments are from the October 1999 *DRAFT Guidance for Industry: Applications Covered by Section 505(b)(2)*, available at <http://www.fda.gov/cder/guidance/guidance.htm>

1. 505(b)(2) applications must clearly identify those portions of the application that rely on information you do not own or to which you do not have a right of reference.

2. A 505(b)(2) application that relies upon the Agency's previous finding of safety or efficacy for a listed drug must specifically identify any and all listed drugs by established name, proprietary name, dosage form, strength, route of administration, name of the listed drug's sponsor and the application number.
3. A 505(b)(2) application relying upon literature must clearly identify the listed drug(s) on which the studies were conducted (if any).
4. For a 505(b)(2) application you must provide a patent certification or statement as required under section 505(b)(2) of the Act with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed or other drug (21 CFR 314.54(a)(1)(vi)). -- (Listed in the Orange Book)
5. Patent certification should specify the exact patent number(s), and the exact name of the listed drug or other drug even if all relevant patents have expired.
6. Note the following key issue regarding the requirement for appropriate patent certification: Due to legislation contained in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), if during the review of an NDA filed under 505(b)(2), either the applicant decides to refer to a different product than that/those identified in the original application, or the Agency discovers that the applicant did not appropriately certify to the patent(s) of the products referenced in the original application, then the applicant would be required to withdraw and resubmit the application as a new original NDA, with the appropriate Patent Certifications included, potentially requiring a new User Fee.

### **Discussion**

**The Sponsor agreed to provide safety qualification for the level of exposure to (b) (4) found in the product formulation.**

2. According to the 505(b)(2) route, we are proposing a literature-evidence basis for the non-clinical part of the NDA. Does the Agency accept this approach?

#### **FDA Response**

No. Although data from the literature may be used to provide nonclinical support for a 505(b)(2) application, the different absorption profile (i.e. lower in the GI tract) when compared with the approved immediate-release product would require that a 90-day bridging toxicity and toxicokinetic study be conducted in the dog. This study should be completed and the results submitted prior to conducting Phase 3 clinical studies.

## Discussion

**The Sponsor is to provide information on the results of the pharmacology/toxicology study in dogs and address the potential for previously uncharacterized toxicity due to absorption [REDACTED] (b) (4). This concern could be addressed by completion of a 90-day bridging toxicity study in the dog model with toxicokinetic data collected, following the use of the final study drug clinical formulation in dogs. The Sponsor understood the concern expressed by the Division; however, they noted that they were aware of other drugs on the market that released glucocorticoids [REDACTED] (b) (4). They proposed to address the Division's concern by providing data regarding the potential for unique toxicity in lieu of conducting a separate animal study. The Division noted that this option may be adequate to address the concern and agreed to further discussion of the issue with the Sponsor following review of the materials compiled.**

3. To complete a 505(2) application, a PK-PD modeling program, as described in the briefing package will be done. Does the Agency agree with this approach?

### FDA Response

You may conduct PK-PD modeling to support the application. However, only a concept was provided in the package. As such, the Division cannot provide additional feedback at this time. You may submit details of the approach for further comment.

Although, studies EMR 62215-001 and -002 conducted with developmental formulations are useful in understanding the pharmaceutical development aspects, study EMR 62215-005 conducted with the final formulation will be the most relevant.

Since you are proposing to submit a 505(b)(2) application, relying on the findings of efficacy and safety on a previously approved US product, a relative bioavailability study comparing your product to a listed product in the Orange Book should be submitted. It appears that you are relying on *in vitro* dissolution data to provide the linkage between Decortin<sup>®</sup> 5 mg (European product) used in study EMR 62215-005 and an approved US product (Watson Labs 5 mg). However, the adequacy of this cannot be ascertained at this time in the absence of a side by side formulation composition comparison of the Decortin<sup>®</sup> and Watson Labs 5 mg products, and a review of the dissolution data (and the appropriateness of the dissolution method).

Although information on the food effect seems to be available, clarify whether a high fat meal, as defined in the FDA guidance for food effect, was used. Further, clarify whether the pharmacokinetics of the final product was characterized under fasting conditions. Study 62215-005 included only a concurrent fed arm and another arm where the product seems to have been administered three hours after a light meal. Clarify whether [REDACTED] (b) (4) so as to conclude that food effect information acquired for the 5-mg strength can be applied to the lower strengths (1-mg and 2-mg tablets) as well.

Since this is a new product, its pharmacokinetic characterization should be complete; pharmacokinetic information should be provided for the 1-mg and 2-mg strengths and not just for the 5-mg strength (i.e., dose proportionality information in the proposed dosage regimen is needed). In addition, multiple-dose pharmacokinetics using the proposed dosage regimen should be characterized.

Finally, investigate the susceptibility of your product to alcohol interaction (*in vitro* release may be performed initially, followed by *in vivo* study if needed).

### **Discussion**

**The Sponsor agreed to provide PK-PD modeling. The Division asked whether the data originated from the completed study, Study EMR 62215-005. The Sponsor responded that the data was from healthy volunteers only, with the active substance obtained from a supplier of an approved drug.**

**The Division expressed concern that, although the drug substance is the same as the approved product, the formulation is different and, therefore, has an unknown safety profile. Additionally, because the drug release and, therefore, the absorption are at a different anatomical (b) (4) there is the potential for additional local toxicity with this formulation.**

**The Sponsor agreed to provide PK information on the exposure of this drug in a representative American population.**

**With respect to 505(b)(2) and relative bioavailability linkage, the Sponsor is to provide dissolution data and formulation composition information on Decortin 5 mg and Watson Labs 5-mg tablets. Additionally, the Sponsor will submit PK information on all three strengths of the drug, i.e., 1 mg, 2 mg and 5 mg.**

**The Sponsor confirmed with the Division that a high fat diet was used to show food effect. No PK data was available during fasting, because a daytime 10-hour fast was impractical to conduct. The Division suggested that perhaps the Sponsor could conduct a food effect study in which the subjects would be dosed in the morning following an overnight (10 hours) fast.**

**Regarding the formulation, the Division suggested dose proportionality and a multiple dose PK study. The Sponsor stated (b) (4) and will submit all necessary information regarding BCS Classification 1 for the drug product (formulation, solubility, etc). It is the Sponsor's intention to provide justification for not obtaining PK information for the**

**1- and 2-mg strengths. As part of the BCS classification package, the Sponsor was asked to provide information on the permeability of the product.**

**The Sponsor informed the Division that the *in vitro* alcohol interaction study had already been initiated and the results will be forwarded when available.**

4. Does the Agency agree that the development plan supports the proposed indication “for the treatment of Rheumatoid Arthritis?”

FDA Response

The Agency has previously granted the claim for the “treatment of the signs and symptoms of rheumatoid arthritis” based on an accepted measure of clinical efficacy, the ACR 20 criteria. As noted in the *Guidance for Industry, Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA)*, available at <http://www.fda.gov/cder/guidance/guidance.htm>, the Agency recommends using either the ACR 20 or a subset of the ACR 20, as previously recommended in the 1988 *Guideline for the Clinical Evaluation of Anti-inflammatory and Antirheumatic Drugs* (FDA 1988). The primary measures are: joint counts (pain, tenderness, and swelling), and global assessments (physician and patient). The remaining measures are considered secondary efficacy variables: duration of morning stiffness, grip strength, time required to walk 50 feet, and the erythrocyte sedimentation rate.

Clarify how you will accurately measure the extent of morning stiffness and how you will define a clinically meaningful difference in morning stiffness between the two treatment groups. You are reminded that morning stiffness is not one of the measures of efficacy in the ACR 20.

(b) (4)

Clarify the following issues:

- 
- 
- 

(b) (4)

Clarify the blinding procedures in protocol EMR 62215-003, specifically, how you propose to ensure that a patient entering the study on a given dose of prednisone ( $\leq 10$  mg per day), stays on that prednisone dose and remains blinded to the clinical investigator.

A superiority claim of 27% is proposed in protocol EMR 62215-003. The Agency reminds you that, should any superiority claim be granted, you would need to provide replicate evidence of efficacy.

We acknowledge Amendment No. 1, proposed protocol EMR62215-003, to add a subgroup (N=32 patients) which would undergo three Corticotropin-Releasing Hormone (CRH) Tests during the study (at baseline, after the double-blind phase, and after conclusion of the 9-month, open-treatment phase) to monitor the hypothalamic pituitary axis (HPA). If there is a difference in the HPA outcome results between the treatment groups, you may need long-term safety data to support LODOTRA™ drug development and an NDA application, or a rationale as to why additional safety data would not be necessary. The Division is not aware of acceptable criteria to compare outcome results between steroid doses and formulation with respect to the HPA axis suppression.

The proposed Phase 3 protocol EMR 6215-003 is currently being conducted in two countries, Germany and Poland. Nitec Pharma states in the cover letter of this PIND, that it "...does not plan to conduct any U.S. studies prior to submission of the NDA." The Agency reminds you that, should drug development continue for LODOTRA™ in the U.S., a representative American population would need to be investigated or a rationale provided for why these investigations are not needed in the context of an RA population.

Though the Division acknowledges that protocol EMR 62215-003 enrolled the first subject in April 2004, completed the double-blind phase in May 2005, and the open-follow-up phase in February 2006, clarify if osteocalcin is being measured in protocol EMR 62215-003. Osteocalcin is listed in the standard parameters to be investigated (page 23, briefing book); however, it is not included in the laboratory section of the protocol, nor in the study schedule table. Of note, a threshold laboratory value was not provided for the exclusion criteria "severe hepatic involvement."

### **Discussion**

**The Sponsor reported on patient feedback regarding the prevalence of morning stiffness, as discussed at OMERACT and other rheumatology meetings. The sponsor further explained that they are not seeking** (b) (4)

**The Division responded that the Agency** (b) (4)  
**would be reluctant to support such an indication without additional information, internal discussions, and perhaps input from the Arthritis Advisory Committee. The Division discussed that, perhaps Nitec could develop its product for the relief of signs and symptoms of RA using the standard endpoints, and then add morning stiffness as a secondary outcome.** (b) (4)

**however, the Division's position on utilizing the results of a secondary outcome would depend on the strength of the results.**

**The Sponsor argued** (b) (4)

(b) (4)

**The Division asked the Sponsor to provide literature that would support**

(b) (4)

#### ADDITIONAL CMC COMMENT

Please request a CMC EOP2 meeting to discuss the CMC drug development program as discussed in FDA's *Guidance for Industry: INDs for Phase 2 and Phase 3 Studies, Chemistry, Manufacturing, and Controls Information* (<http://www.fda.gov/cder/guidance/3619fnl.doc>).

#### Discussion

**There was no further discussion.**

#### ACTION ITEMS

- 1. The Sponsor agreed to provide safety qualification for the level of exposure to (b) (4) found in Sponsor's product formulation.**
- 2. The Sponsor will submit the results of the pharmacology/toxicology study in dogs and address the Agency's concern regarding the potential for unique local toxicity (b) (4) with the IND submission.**
- 3. The Sponsor agreed to provide PK-PD modeling.**
- 4. The Sponsor agreed to provide information on the exposure of the drug in the American population.**
- 5. The Sponsor will provide an entire PK report on all three strengths of the drug (e.g., formulation information on 3 dose strengths, dissolution data on Decortin and Watson 5 mg tablets, etc.)**
- 6. Additionally the Sponsor will provide BCS Classification 1 data, including the permeability information for the product.**

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/s/

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Paul Balcer

4/21/2006 06:16:24 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 72,569

Nitec Pharma  
(c/o) Aclairo  
8230 Leesburg Pike, Suite 620  
Vienna, VA 22182

Attention: Dana Dunn, MS  
US Agent

Dear Ms. Dunn:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Lodotra (prednisolone modified release tablet).

Attached are the Division's responses to the questions from your meeting package for our upcoming End-of-Phase 2 meeting, scheduled for December 13, 2007, to discuss the development of this product and progress made to date. Your questions are in italics and the Division's responses are in bold.

The previously agreed upon time is still set aside to meet with you, but, if you would like to either cancel the meeting, because you feel all your questions have been answered to your satisfaction, or re-focus the meeting (i.e., only focus on items which you feel require additional clarification), that would be acceptable to the Division as well.

We will be happy to provide clarification on any of the Division's responses, but **WILL NOT entertain any NEW questions, topics or review additional data** (there is simply not enough time prior to the meeting for the team to review such materials). Please let me know if you would like to change anything about our forthcoming meeting.

If you have any questions, please call me at 301-796-2205.

Sincerely,

*{See appended electronic signature page}*

Kathleen Davies, MS  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**SPONSOR MEETING AGENDA**

**MEETING DATE:** December 13, 2007

**TIME:** 3:30 PM – 5:00 PM (EST)

**LOCATION:** Food and Drug Administration, Bldg. 22, Room 1309  
 10903 New Hampshire Ave., Silver Spring, MD 20993-0002

**APPLICATION:** IND 72,569

**PRODUCT:** Lodotra (prednisolone modified release tablet)

**INDICATION:** Treatment of RA

**SPONSOR:** Nitec Pharma <sup>(c/o)</sup> Aclairo

**TYPE OF MEETING:** End-of-Phase 2, Type B

**MEETING CHAIR:** Jeffery Siegel, MD, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

**MEETING RECORDER:** Kathleen Davies, MS, Regulatory Health Project Manager

<b>FDA Attendees</b>	<b>Title</b>
Bob Rappaport, MD	Director, Division of Anesthesia, Analgesia and Rheumatology Products
Rigoberto Roca, MD	Deputy Director (Rheumatology Team)
Jeff Siegel, MD	Clinical Team Leader
Carolyn Yancey, MD	Clinical Reviewer
Ali Al Hakim, PhD	Chief, Branch II, Office of New Drug Quality Assessment
Danae Christodolou, PhD	Pharmaceutical Assessment Lead
Dan Mellon, PhD	Pharmacology/Toxicology Supervisor
Asoke Mukherjee, PhD	Pharmacology/Toxicology Reviewer
Suresh Doddapaneni, PhD	Clinical Pharmacology Team Leader
David Lee, PhD	Clinical Pharmacology Reviewer
Dionne Price, PhD	Biostatistics Team Leader
Joan Buenconsejo, PhD	Biostatistics Reviewer
Kathleen Davies, MS	Regulatory Health Project Manager
<b>Nitec Pharma</b>	<b>Title</b>
Achim Shchaffler, PhD	E VP Research and Development
Stephan Witte, PhD	VP Global Clinical Development
Hans Rensland, PhD	VP Global Regulatory Affairs
Markus Vogt, PhD	VP Global Quality and Compliance
Dana Dunn, MS	Authorized US Representative
(b) (4)	US Consultant: Toxicology
(b) (4)	US Consultant: Regulatory Affairs

(b) (4)	US Consultant: Clinical Development
(b) (4)	US Consultant: Statistics
(b) (4)	US Consultant: PK Studies

## BACKGROUND

Nitec has submitted an End-of-Phase 2 Type B meeting request for Lodotra, a modified release tablet of prednisolone for treatment of RA. Nitec plans to submit their NDA in 2009 and would like concurrence and agreement on the ongoing development of their product. Specifically, Nitec would like agreement on the design of a planned multi-national Phase 3 study.

### I. Clinical Development Program

*Question 1. If the results of the CAPRA-2 (#NP01-007), based on the ACR criteria, meet statistical significance, does the Agency agree that the design of this study is adequate to support the following labeling claim:*

*“...indication in adults for the treatment of rheumatoid arthritis to reduce signs and symptoms, ...”?*

#### FDA Response:

**Your proposed Phase 3 clinical protocol (# NP01-007) for the proposed indication** (b) (4)

**studies 5 mg Lodotra® once daily or matching placebo, with patients randomized 1:1 for a 12-week treatment period. Patients treated with glucocorticoids within 6 weeks prior to screening would be excluded from this study. The primary efficacy endpoint would be the ACR20 response rate and the key secondary endpoint would be the relative change in the duration of morning stiffness assessed using patient diaries.**

**Your completed Phase 3 clinical study (#EMR62215-003) enrolled patients who continued on fixed doses of corticosteroids, 2.5 mg to 10 mg, for at least 3 months, with stable doses for at least 1 month prior to screening. The pre-specified primary efficacy endpoint was the duration of morning stiffness based on patient diaries after 3 months expressed as relative changes from baseline. You report that this study demonstrated statistical significance for the duration of morning stiffness but no difference in ACR20 responders after 12 weeks of treatment.**

**In principle, within the context of a 505(b)(2) application, if your Phase 3 *synopsis* clinical protocol study (# NP01-007) demonstrates statistically significantly more ACR20 responses with Lodotra, such a study would support a proposed labeling claim of “reducing signs and symptoms of RA” since the approved labeling for prednisone contains an indication of rheumatoid arthritis.**

*Question 2. Does FDA agree that an NDA registration package for Lodotra based upon safety and efficacy results from the two Phase 3 studies described above, namely, the proposed CAPRA-2 study in addition to the completed EU CAPRA-1 study, is adequate for submission and review?*

**FDA Response:**

**In principle, within the context of a 505(b)(2) application, if your proposed Phase 3 study (# NPO1-007) demonstrates improvement in signs and symptoms in RA, then study # NPO1-007 alone could support submission of a NDA registration package for Lodotra for signs and symptoms of RA. You propose also submitting an additional study (# MR62215-003) [REDACTED] (b) (4) which is acceptable.**

*See response to Question # 1.*

*See response to Question # 3.*

*Question 3. Does FDA agree that an improvement in morning stiffness if supported by the results from the completed EU study CAPRA-1 and the proposed CAPRA-2 study may be considered as a component of a possible labeling claim for Lodotra?*

**FDA Response:**

**You will need to provide substantial evidence to support a new labeling claim of “improvement in morning stiffness” for Lodotra, which ordinarily means at least two adequate and controlled trials. Assuming you have adequate data to support a claim of improving “the signs and symptoms in RA,” if your completed EU study (# MR62215-003) CAPRA-1 and your proposed clinical protocol (# NPO1-007) CAPRA-2 both support efficacy for improvement in morning stiffness, then a labeling claim of “improvement in morning stiffness” could be considered.**

**The exact wording of such a claim would be a review issue.**

*See response under Question # 1.*

*Question 4. Does FDA have any comments about this initial version of the TPP, especially with respect to sections 1. “Indications and Usage,” 2. “Dosage and Administration,” and 14. “Clinical Studies” ?*

*In this version of the TPP, the indication states: [REDACTED] (b) (4)*

**FDA Response:**

**In general terms, the proposed Indication section in the proposed target product profile (TPP) appears reasonable. However, it is likely that the claim of improvement in morning stiffness will be described in the Clinical Studies section and not in the Indication section. The TPP text for the “Dosage and Administration” section would be dependent on the clinical safety and efficacy of your completed clinical studies in RA patients. If your clinical development program is successful, it would, in principle, support text similar to what you have submitted in your meeting package. You propose including [REDACTED] (b) (4) [REDACTED] in the Clinical Studies section. If evidence**

suggests that the (b) (4) provide important information then they may be included in the Clinical Pharmacology section of the package label but not in the Clinical Studies section.

*Question 5. Does FDA agree that these exposure data are adequate to support the submission and review of an NDA registration package for Lodotra?*

**FDA Response:**

**In principle, the size of the EU CAPRA-1 study (# EMR62215-003) and the proposed size of the CAPRA-2 study (# NP01-007) would provide adequate exposure data for your new formulation. However, if on review of the complete safety data, new signals are identified, then additional safety data may be required.**

*Question 6. Does FDA have any comments about the proposed initial version of the TPP especially with respect to sections 4. "Contraindications," 5. "Warning and Precautions," and 6. "Adverse Reactions" ?*

**FDA Response:**

**You should review to the most recently approved immediate-release prednisone label and make sure all appropriate information is included in these sections of your TPP. At this time, the Division has no additional comments about the proposed TPP.**

## **II. Bioavailability and Pharmacokinetics**

*Question 7. Does the Agency agree that the information provided above is sufficient to waive the need for Bioequivalence study of US and EU reference prednisone product?*

**FDA Response:**

**Overall, adequate information seems to have been provided linking Decortin with US approved products Watson Labs, Mutual Pharm, and Roxane.**

*Question 8. Does the Agency agree that the information provided herein and in the waiver provided in the EoP2 BP Attachment 10 is sufficient to waive the need for a multiple-dose study on this product?*

**FDA Response:**

**Based upon the data provided in the meeting package, a multiple-dose study for this product is not required.**

*Question 9. Does the Agency agree that the results of the studies listed provide sufficient evidence of this product's pharmacokinetic properties, and are sufficiently complete to submit a 505(b)(2) application for this product?*

**FDA Response:**

**The Division agrees that the results of the studies listed provide sufficient evidence of PK to submit a 505(b)(2) application.**

*Question 10. Based on this ongoing development program, does FDA have any comments on the initial draft version of the Target Product Profile for this product (see EoP2 BP Attachment 3), especially section 12, "Clinical Pharmacology"?*

**FDA Response:**

**See the response to Question # 4 for comment concerning [REDACTED] (b) (4) reported results.**

**III. Nonclinical**

*Question 11. Does the FDA agree that the clinical safety information for Lodotra and oral prednisone is adequate to waive the 90 day bridging toxicology study in the dog, as justified by the waiver presented in attachment 11?*

**FDA Response:**

**The Division agrees that the clinical safety information for Lodotra and oral prednisone is adequate to waive the 90-day bridging toxicology study.**

*Question 12. Does the Agency agree that based on the extensive clinical safety experience with Lodotra, the 3-month dog bridging toxicity study can be completed in parallel with the conduct of the CAPRA-2 study?*

**FDA Response:**

**See Question 11.**

*Question 13. Does the FDA agree that sufficient information was provided in the IND with respect to the safety qualification for the level of [REDACTED] (b) (4) used in the product?*

**FDA Response:**

**The Division agrees that sufficient information was provided in the IND with respect to the safety qualification of [REDACTED] (b) (4)**

**IV. Chemistry, Manufacturing and Controls**

*Question 14. Does the Agency agree to the proposed specifications for Lodotra as per Attachment 14?*

**FDA Response:**

**Modify your impurities and degradents specifications as per ICH Q3A and Q3B for the NDA.**

**Dissolution: Provide additional sampling time points, e.g. intermediate between t=0 and 450 minutes or justification to the contrary. The proposed dissolution specification will be assessed upon review of in-vitro dissolution profiles at release and on stability of primary and clinical batches. Provide in-vitro dissolution data to support robustness and discriminatory ability of the dissolution method.**

*Question 15. Does the Agency agree that this add-line drug release test will serve as an adequate in-process control to assure appropriate lag time targeting?*

**FDA Response:**

**Provide justification for this proposal in the NDA, e.g., by including supporting data from developmental, clinical and primary batches that demonstrate correlation of the force to the resulting dissolution lag time.**

*Question 16. Does the Agency agree to the proposed design of stability studies in the child resistant container according to Attachment 16?*

**FDA Response:**

**This proposal is acceptable.**

*Question 17. Does the Agency agree that the second supplier (b) (4) may be qualified based on stability data from forced degradation studies and on stability data from the patient friendly primary packaging containers as described above?*

**FDA Response:**

**No. In addition to stress degradation studies and drug product stability data, provide acceptance specifications for the drug substance by the drug product manufacturer. These specifications should be used as future drug substance manufacturer qualifying criteria.**

**Provide batch release and stability data for drug product manufactured from prednisone sourced from both suppliers and used in Phase 3 studies.**

*Question 18. Will FDA accept a waiver for an environmental assessment on this product?*

**FDA Response:**

**Provide a request for categorical exclusion from an environmental assessment in the NDA as per 21 CFR Part 25.31(a).**

*Question 19. Does FDA have any comments about the proposed initial version of the TPP, especially with respect to section 3. "Dosage Forms and Strengths," 11. "Description," and 16. "How Supplied/Storage and Handling"?*

**FDA Response:**

**Include the following information, as applicable:**

**3. Dosage Forms and Strengths:**

Available dosage form, e.g., tablets, strengths in metric units, active moiety expression of strength, and a description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring and imprinting.

**11. Description:**

Proprietary and established name, dosage form and route of administration, active moiety expression of strength, inactive ingredient information listed by USP/NF names in alphabetical order (USP <1091>), pharmacological/therapeutic class, chemical name, structural formula, molecular weight, and any other important chemical property, e.g., pKa or pH.

**16. How Supplied/Storage and Handling**

Strength of dosage form, available units (e.g., bottles of 100 tablets), identification of dosage forms, (e.g., shape, color, coating, scoring, imprinting), NDC number.

Special handling, e.g., protect from light; storage conditions, “store at XX°C, excursions permitted XX°C to XX°C (XX° to XX°F)”.

**V. Administrative**

*Question 20. Does FDA agree [REDACTED] <sup>(b) (4)</sup> pediatric studies for Lodotra?*

**FDA Response:**

In accordance, with the requirements of Titles IV and V of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Pub. L. No. 110-85, 121 Stat. 823), the Pediatric Review Committee (PeRC) must review all Pediatric Assessments, Pediatric Plans, and Waiver and Deferral requests. It is premature for the Division to agree with such a request at this point.

**Additional Comments**

- 1. Submit the full protocol for CAPRA-2 that includes a detailed description of your proposed statistical analysis.**
- 2. In the protocol synopsis (# NP01-007), you propose to employ the last observation carried forward (LOCF) approach to impute missing data for the primary endpoint (i.e. ACR20 responder). The Division recommends that any subject who drops out of the study be considered a non-responder.**
- 3. Revise your proposed safety monitoring to include Hemocult testing for fecal blood in the proposed 12-week treatment phase.**
- 4. Submit the sections of your proposed Informed Consent which explain the clinical safety experience of your modified-release prednisone formulation.**

Linked Applications

Sponsor Name

Drug Name

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IND 72569

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NITEC PHARMA

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LODOTRA

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KATHLEEN M DAVIES

12/12/2007

Regulatory Project Manager