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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review Addendum

Date	July 25, 2012
From	Susan Limb, MD
Subject	Cross-Discipline Team Leader Review Addendum
NDA/BLA # Supplement#	NDA 202020
Applicant	Horizon Pharma
Date of Submission	September 26, 2011
PDUFA Goal Date	July 26, 2012
Proprietary Name / Established (USAN) names	Rayos (prednisone)
Dosage forms / Strength	1, 2, and 5 mg delayed-release oral tablet
Proposed Indication(s)	1. Treatment of rheumatoid arthritis in adult patients
Recommended:	*Approval*

1. Executive Summary

This memorandum serves as an addendum to the CDTL review dated July 5, 2012, which recommended approval for NP01, a new delayed-release tablet formulation of prednisone. The proposed tradename is Rayos. The July 5, 2012, CDTL review concluded that the submitted CMC and clinical pharmacology data support the approval of NP01 for the full range of indications which are currently approved for immediate-release prednisone (prednisone IR). The submitted rheumatoid arthritis (RA) clinical trial data, while not necessary for approval, were deemed generally supportive of the efficacy and safety of prednisone. Therefore, the July 5, 2012, review recommended that clinical trial data relevant to the primary endpoint be included for the sake of description but did not support the addition of information based on secondary endpoints. Reasons cited for the omission of various secondary endpoints included a lack of replication, the absence of multiplicity adjustment, and the uncertain clinical relevance of several secondary efficacy variables.

While the recommended regulatory action of approval for the application remains unchanged, further discussion regarding the regulatory precedent for the labeling of other RA products has let to a modification of the CDTL review's original labeling recommendations. To maintain consistency with other products approved for RA, the CDTL review finds the inclusion of morning stiffness data, the prespecified secondary endpoint, to be acceptable. The morning stiffness treatment effect in minutes should be included to aid in the clinical interpretation of the result. (b) (4) and disclaimer language stating that the efficacy of NP01 compared to prednisone IR has not been established is still recommended. Further discussion of the label and the regulatory precedent can be found in the Division Director Memorandum dated July 25, 2012. As stated above, the recommended regulatory action is approval.

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SUSAN L LIMB
07/25/2012

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1. Introduction

Horizon Pharma submitted a 505(b)(2) New Drug Application (NDA) 202020 on September 25, 2011, for NP01, a new dosage form of prednisone formulated as 1, 2, and 5 mg delayed-released oral tablets, originally proposed for the treatment of rheumatoid arthritis in adult patients. The proposed tradename is Rayos. The application references immediate-release prednisone (PrediSONE Tablets; ANDA 87800 and 80352, Roxane Labs), which is approved for a broad range of indications, including the treatment of rheumatoid arthritis (RA). Since immediate-release prednisone (prednisone IR) already has an indication for the treatment of RA, CMC and clinical pharmacology data would generally have been adequate to support a new formulation of prednisone. However, the Applicant submitted data from a placebo-controlled clinical trial to support an RA indication (b) (4) including the reduction of morning stiffness. Upon review, the clinical data support a general RA treatment indication as expected but do not provide adequate support for (b) (4) Aside from the differences in pharmacokinetics, the efficacy and safety profile for NP01 appear similar to that of prednisone IR. No clinically meaningful differences between NP01 and prednisone IR were identified that would warrant inclusion in labeling. Therefore, the review team has recommended that NP01 be granted the full range of indications which are currently approved for prednisone IR with similar labeling.

This memo provides an overview of the development program and regulatory history, summarizing the CMC and clinical pharmacology data which are sufficient to support approval of NP01 for the full range of indications. The memo also presents the major results of the clinical program, focusing on the inadequacy of the clinical trial data to support new labeling claims beyond those already approved for prednisone IR.

2. Background

Prednisone and the treatment of rheumatoid arthritis
Prednisone was first used to successfully treat rheumatoid arthritis (RA) in the late 1940's and is now used to treat a range of diseases associated with an inflammatory component. Oral, immediate-release prednisone (prednisone IR) is widely available as a generic drug and is approved for multiple inflammatory arthritides and other inflammatory, non-rheumatologic conditions as follows:

- allergic conditions: atopic dermatitis, drug hypersensitivity reactions, seasonal or perennial allergic rhinitis, serum sickness
- dermatologic diseases: bullous dermatitis herpetiformis, contact dermatitis, exfoliative erythroderma, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome)
- endocrine conditions: congenital adrenal hyperplasia, hypercalcemia of malignancy, nonsuppurative thyroiditis, primary or secondary adrenocortical insufficiency
- gastrointestinal conditions: Crohn's disease, ulcerative colitis
- hematologic diseases: acquired (autoimmune) hemolytic anemia, Diamond-Blackfan anemia, idiopathic thrombocytopenic purpura in adults, pure red cell aplasia, secondary thrombocytopenia in adults
- neoplastic conditions: acute leukemia, aggressive lymphoma
- nervous system conditions: acute exacerbations of multiple sclerosis, cerebral edema associated with primary or metastatic brain tumor, craniotomy or head injury
- ophthalmic conditions: sympathetic ophthalmia, uveitis and ocular inflammatory conditions unresponsive to topical steroids
- conditions related to organ transplantation: acute or chronic solid organ rejection
- pulmonary diseases: COPD, allergic bronchopulmonary aspergillosis, aspiration pneumonia, asthma, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate chemotherapy, hypersensitivity pneumonitis, idiopathic bronchiolitis obliterans with organizing pneumonia, idiopathic eosinophilic pneumonias, idiopathic pulmonary fibrosis, pneumocystis carinii pneumonia (PCP) associated with hypoxemia, occurring in an HIV+ individual who is also under treatment with appropriate anti-PCP antibiotics, symptomatic sarcoidosis
- renal conditions: to induce diuresis or remission of proteinuria in nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus

- rheumatologic conditions: acute gouty arthritis, ankylosing spondylitis, dermatomyositis/polymyositis, polymylagia rheumatica, psoriatic arthiritis, relapsing polychondritis, rheumatoid arthritis including juvenile rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, vasculitis

- specific infectious conditions: trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block used concurrently with appropriate antituberculous chemotherapy

The reference drug label (PredniSONE Tablet, Roxane Labs) states that prednisone is indicated as adjunctive therapy for short-term administration or low dose maintenance therapy of rheumatoid arthritis including juvenile rheumatoid arthritis (juvenile inflammatory arthritis). Given the well-known adverse effects of chronic systemic corticosteroids and the introduction of newer, highly effective therapeutic agents for RA, most notably the disease-modifying anti-rheumatic drugs (DMARD) like tumor necrosis factor (TNF) inhibitors, the use of prednisone in the treatment of RA is now diminished.

Rationale for a delayed-release prednisone formulation
In general, prednisone is typically administered in the morning to coincide with the circadian pattern of adrenal cortex activity in order to minimize the suppression of adrenocorticoid activity, as noted in the current PredniSONE label. Certain RA symptoms such as joint pain and stiffness also exhibit a circadian pattern, presumably secondary to elevated levels of pro-inflammatory cytokines in the early morning. Horizon contends that typical AM administration of prednisone IR is not synchronized with this early-morning cytokine rise that occurs prior to patient awakening. To address this diurnal variability in cytokine release, Horizon developed a delayed-release prednisone formulation to be taken once daily at bedtime, designed to release prednisone in the early-morning hours without compromising patient convenience. Horizon postulates that the earlier administration of daily prednisone will result in more efficacious treatment of RA symptoms, particularly the symptom of early morning stiffness.

Regulatory history

- **March 24, 2006, Pre-IND with the Division of Anesthesia, Analgesia, and Rheumatology (DAARP):** (b) (4) The sponsor described its ongoing European development program, comprised of bioavailability trials comparing NP01 to an EU-approved prednisone IR formulation (Decortin) and a clinical trial comparing NP01 to Decortin with morning stiffness as a novel primary endpoint. The Division confirmed that a 505(b)(2) pathway was appropriate (b) (4) The Division suggested that the sponsor consider pursuing a general RA treatment indication based on a standard RA endpoint such as the ACR20 (American College of Rheumatology response criteria for 20% improvement) with morning stiffness as a secondary outcome, adding that the acceptability of morning stiffness as a secondary claim would be a review issue.

Of note, there was internal disagreement within the review division at that time regarding the validity of a specific morning stiffness claim for RA, given that any therapy with a general RA treatment indication would be expected to have anti-inflammatory effects that would improve morning stiffness, among multiple other signs and symptoms. For example, morning stiffness is generally not an issue for patients appropriately treated with TNF inhibitors. In addition, it was noted that morning stiffness is highly variable, subjective, and is associated with other musculoskeletal conditions, making its measurement specific to RA challenging. For this reason, morning stiffness is not included as a component in the ACR20 or in the DAS28 (Disease Activity Score Calculator for Rheumatoid Arthritis), another standard composite score used for assessing RA disease activity. Finally, there are no validated PRO instruments for assessing morning stiffness.

- **December 13, 2007, End-of-Phase 2 meeting with DAARP:** By the time of this meeting, the European active-controlled trial was complete. In response to the Division's advice at the Pre-IND meeting in 2006, the sponsor proposed to conduct an additional Phase 3 trial, a placebo-controlled trial with ACR20 response rate as the primary endpoint and patient-reported morning stiffness as a key secondary endpoint. The Division stated that the proposed program appeared reasonable to support a general RA treatment indication but that the acceptability of morning stiffness as a secondary claim in the label would be a review issue. The Division stated that replication of benefit from at least two adequate, well-controlled trials was expected to support such a new secondary claim for morning stiffness. As noted for the Pre-IND meeting, the formal comments conveyed to the sponsor did not necessarily reflect scientific consensus within the Division, as concerns regarding the validity of a morning stiffness claim remained. Other issues discussed during this meeting included the use of in vitro data to bridge Decortin, the prednisone IR formulation used in the bioavailability trials, to a US-approved prednisone IR formulation.

- **January 26, 2010, Pre-NDA meeting with DAARP:** The Division confirmed that positive ACR20 results from the placebo-controlled Phase 3 trial would support a general RA treatment indication given the established efficacy and safety profile of prednisone IR for RA. The Division stated that morning stiffness data, presuming replicate, positive results from both the active-controlled and placebo-controlled trials, may be included in the Clinical Studies section of the label pending review. The Division requested that the sponsor include validation of the morning stiffness patient-reported outcome (PRO) in the application and referred to the *Guidance for Industry, Patient-reported outcome measures: Use in medical product development to support labeling claims* (December 2009).

- **September 25, 2011, NDA submission to the Division of Pulmonary, Allergy, and Rheumatology (DPARP)**

3. CMC/Device

The recommended action from a CMC perspective is Approval pending a satisfactory establishment evaluation report.

- **General product quality considerations**

The drug product consists of an immediate release prednisone core tablet that is surrounded by an inactive tablet shell. All excipients used are common for tablets. Drug release is triggered by penetration of water into the outer tablet shell, (b) (4) After a delay time of approximately (b) (4) hours, the tablet shell opens into two halves and the core tablet then releases the prednisone active similarly to an immediate release tablet. (b) (4) .

The total tablet weighs 410 mg, (b) (4) The final round tablet is 9 mm in diameter and 5 mm thick. The tablet is manufactured in three strengths: 1 mg, 2 mg, and 5 mg. The tablet strengths are distinguished from one another by both color and debossing (b) (4) as defined by the *Guidance for Industry: Bioavailability and bioequivalence studies for orally administered drug products – general considerations* (March 2003).

Stability data support a product expiry period of 30 months under the following labeled storage conditions: "Store at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF)." The product is photo labile and requires a container closure system that is light-protective.

- **Facilities review/inspection**

The final recommendation from the Office of Compliance remains pending at the time of this memorandum. The prednisone drug substance is manufactured by Tianjin Tianyao (Tianjin, China). The drug substance DMF was deemed adequate. The drug product is manufactured by Bayer Pharma AG (Germany) or Aenova France SAS (France). Both sites have acceptable EES status.

- **Other notable issues (resolved or outstanding)**

None.

4. Nonclinical Pharmacology/Toxicology

The recommended action from a Nonclinical Pharmacology/Toxicology perspective is Approval. There are no outstanding nonclinical issues.

No new nonclinical studies were submitted or required. The application relies on the previously approved prednisone labeling. Changes to the proposed labeling are recommended to maintain consistency with related currently approved products. Among these changes, the recommended Pregnancy Category rating is now Pregnancy Category D.

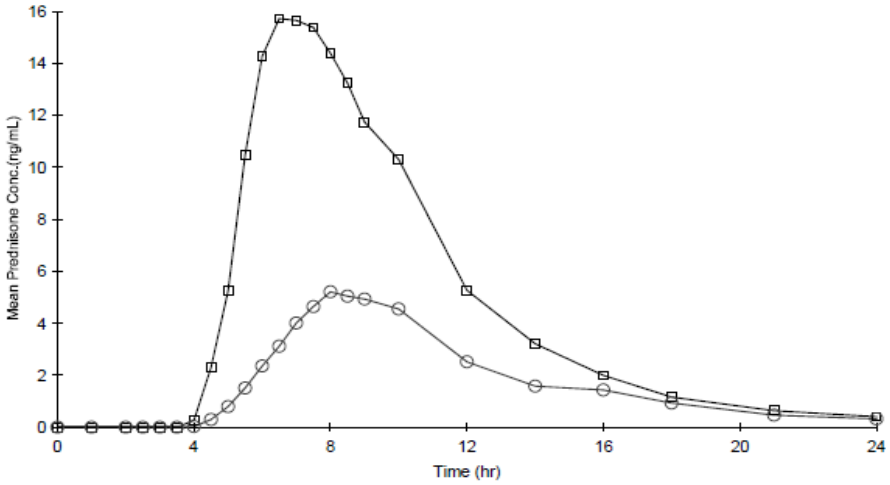
5. Clinical Pharmacology/Biopharmaceutics

The application is deemed acceptable from a Clinical Pharmacology perspective. There are no outstanding issues at this time.

The pharmacokinetic properties of prednisone IR formulations are well known. Prednisone IR is well absorbed following oral administration with an absolute systemic bioavailability averaging 80-100% and a Tmax of 1 to 2 h. Administration with food does not affect the extent of absorption. Prednisone is almost completely metabolized to its active metabolite prednisolone. Systemic levels of prednisolone are 4- to 10-fold higher than those of prednisone. The elimination half-lives for both prednisone and prednisolone are 2-3 hours.

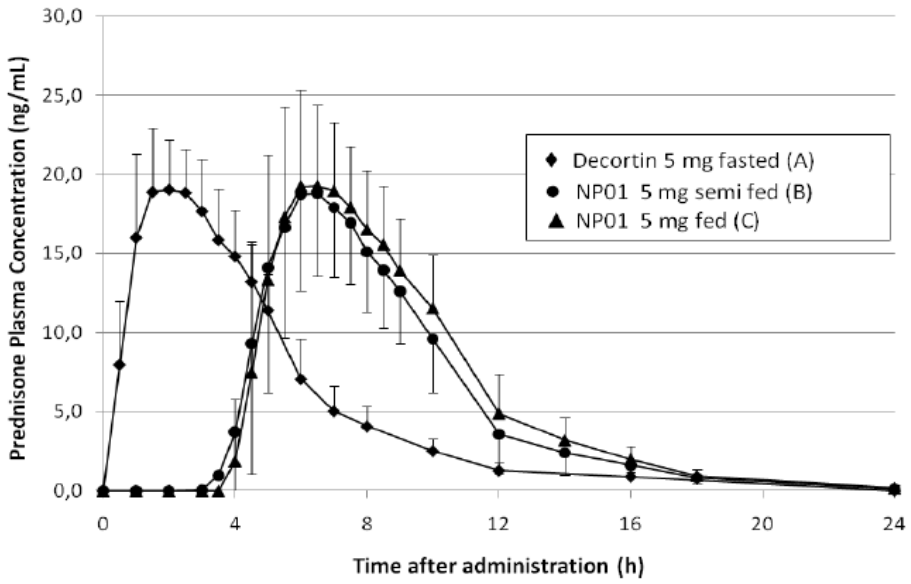
The application includes nine clinical pharmacology and biopharmaceutics studies in adult healthy volunteers to support the characterization of NP01. The following findings are summarized briefly below: 1) NP01 has a pronounced food effect and 2) NP01 has a delayed Tmax compared to IR prednisone. A pronounced food effect was seen after intake of a high-fat meal as compared to fasted conditions (Figure 1). These results show that the Cmax and AUC for both prednisone and prednisolone under fed condition are about three times of those under fasted condition.

Figure 1 Effect of food on pharmacokinetics of NP01 (□– fed state; ○ – fasted state)



Because of a significant food effect of the delayed-release formulation, the Applicant conducted the relative bioavailability study with the IR formulation with NP01 given with food. Under either semi-fasted or fed condition, the exposures of both prednisone and prednisolone from NP01 are comparable to those from prednisone IR under fasted condition (Figure 2). However, the Tmax was delayed 4 hours for NP01 as compared to IR formulation.

Figure 2 Mean plasma profiles for prednisone IR (Decortin) versus NP01 (NP01)



Notably, the exposure of prednisone and prednisolone from prednisone IR (Decortin) was not affected by the intake of food. Based upon the pronounced food effect with NP01, the clinical pharmacology review recommends that labeling specify that NP01 be taken with food.

6. Clinical/Statistical- Efficacy

Overview of the clinical program

The clinical program for NP01 in the treatment of RA is based on two main clinical efficacy and safety trials in RA, a 12-week placebo-controlled trial (NP01-007; Trial 007) and a 12-week active-controlled trial with a 9-month open-label extension period (EMR 62216-003; Trial 003). Of note, the Applicant was unable to provide the required financial disclosure information for the active-controlled trial, Trial 003. The Applicant justified this omission by stating that information from this trial was submitted only in support of safety, not efficacy. As a result, efficacy support for NP01 in the RA indication is based on Trial 007 and the established efficacy profile of prednisone IR; efficacy support (b) (4) relies solely on Trial 007. This approach is inconsistent with prior regulatory advice recommending replicate data to support any new labeling claims.

Table 1 NP01 clinical program					
Trial *Dates*	**Design**	**N**	**Treatment**	**Endpoint**	**Sites**
Controlled trials					
Trial 007 (NP01-007) *5/08-5/09*	12 wk, MC, R, DB, PC, parallel group	231 119	NP01 5 mg q10PM Placebo	1°:ACR20 2°: AM stiffness	62 sites (US, Canada, E. and W. Europe)
Trial 003* (62215-003) *8/04-4/06*	12 wk, MC, R, DB, DD, AC, parallel group	144 144	NP01 3-10mg q10PM Pred IR 3-10 mg q6-8AM	1°: AM stiffness*	17 sites (Germany, Poland)
11/04-1/07	9-mo OLE	249	NP01 3-10mg q10PM		

Pred IR=immediate-release prednisone, MC=multicenter, R=randomized, DB, double-blind, DD=double dummy, PC=placebo-controlled, AC=active-controlled, OLE=open-label extension

* While efficacy measures were assessed, the Applicant submitted Trial 003 only in support of safety, not efficacy.

The application also includes open-label, uncontrolled data from RA patients (LOD9577) and asthma patients (NP01-201) as additional safety information. While these studies expand the overall database of exposures, the limitations of each study relegate these data to secondary support. LOD9577 was a non-interventional postmarketing study conducted in Germany. A total of 2726 patients were enrolled for either 3- or 9-month periods. However, adverse events and other safety parameters were only assessed if conducted as part of the patients' routine medical visits. NP01-201 was an open-label, proof-of-concept trial conducted in 14 asthma patients. Aside from the small sample size, the differences between an RA population and an asthma patient population in terms of baseline demographics, comorbid conditions, and concomitant medications make it difficult to extrapolate the safety results from an asthma population to an RA population. Therefore, while no safety issues of concern were noted upon review of LOD9577 and NP01-201, these studies are not discussed in further detail in this memorandum. More detailed review of these trials can be found in the primary clinical review dated June 22, 2012.

In addition, the application did not include any validation studies to support the use of the morning stiffness patient-reported outcome instrument (PRO) as requested in the January 2010 pre-NDA meeting.

Trial design and endpoint selection: Placebo-controlled trial, Trial 007

Trial 007 (n=350) was a randomized, double-blind, placebo-controlled, 12-week trial comparing the effects of NP01 versus placebo. Patients with moderate to very active RA who had received DMARDs for at least 6 months with a stable dose for at least 6 weeks were randomized 2:1 to NP01 5 mg taken every evening at 10 pm or placebo. Prohibited medications included other corticosteroids, biologic agents, intraarticular injections or synoviorthesis, and initiation of new DMARD or NSAID therapy. The primary endpoint was the ACR20 response at 12 weeks. The change from baseline in duration of morning stiffness at 12 weeks was assessed as a key secondary endpoint. This endpoint was based on patient diary queries where patients were asked to record daily the time of wake-up and the time of

resolution of morning stiffness, the difference being taken as the time to resolution in minutes. Other efficacy variables included the DAS28, and the QoL (SF-36) and fatigue (FACIT-F) questionnaires.

As mentioned previously, there are no validated PRO instruments for the assessment of morning stiffness, and the Applicant did not submit any validation data to support the use of the patient diary queries. These data were requested to address the concerns specific to the instrument raised in an earlier consult from the Agency's Study Endpoints and Label Development team (SEALD). The December 4, 2007, SEALD consult noted a lack of information to support reliability and construct validity and recommended that the Applicant provide scientific justification for a clinically meaningful change and discussion regarding translation and cultural adaptation of the instrument, as outlined in the 2009 PRO guidance. The validation of the instrument is also important given the general concerns regarding the clinical relevance of morning stiffness in the context of currently available, highly effective therapies like biologic agents, which were not permitted in this trial as background therapy.

Efficacy findings

ACR 20 response rates

ACR20 response rates were higher in patients treated with NP01 versus placebo (47% vs. 29%; p=0.001), demonstrating the efficacy of NP01 (Table 2). The positive result is consistent with the established efficacy of prednisone in the treatment of RA treatment. Various sensitivity analyses conducted with different imputations for missing data (observed case, LOCF, withdrawal) were similarly robust.

Table 2 Trial 003: ACR20 response rate at 12 weeks

ACR20 response rate at Week 12 (mITT population; worse case imputation[a])					
NP01 n/N (%)	**Placebo n/N (%)**	**% difference in proportions* (95% CI)**		**Odds ratio (95% CI)**	**P**
108/231 (47)	34/119 (29)	18[b]	17[c] (7, 28)	2 (1, 4)	0.001

[a] worse case imputation: all missing values imputed as non-responders
[b] observed difference
[c] estimate of the treatment difference from the generalized linear model

Duration of morning stiffness

A statistically significant difference was also observed for the relative % change from baseline in the duration of morning stiffness for NP01 vs. placebo (-54% vs. -29%; p<0.001). The median duration of morning stiffness was 46 vs. 79 minutes, respectively.

Table 3 Trial 003: Relative change from baseline in the duration of morning stiffness at 12 weeks (full mITT population)

Relative change from baseline in the duration of morning stiffness at Week 12						
Imputation scheme	**Relative change (%)**				**Difference in median (%) (95% CI)**	**P**
	NP01		**Placebo**			
	N	**Median**	**N**	**Median**		
LOCF	230	-54	119	-27	-20 (-32, -7)	0.0006
BOCF	231	-51	119	-25	-18 (-31, -6)	0.0011

While this result appears supportive, the clinical relevance cannot be confirmed without adequate replication and validation of the instrument as previously discussed. Furthermore, a positive result against placebo is of uncertain clinical value, as one might anticipate any formulation of prednisone to have an effect on morning stiffness via its general effect on RA-association inflammation.

Trial 003 did compare NP01 to prednisone IR and demonstrated a favorable change in morning stiffness (-23 vs. -0.3%), but these efficacy results cannot be relied upon in the absence of the required financial disclosure information as the Applicant acknowledged in the submission. Aside from this issue, there were other concerns with the study results. There were disproportionately more patients in the NP01 group who discontinued early for any reason; of these patients, more patients in the NP01 cited insufficient efficacy as a reason for early discontinuation. There were also major protocol deviations that appear to have impacted the results, including study medication taken out of the specified time range and too short duration of morning stiffness. The morning stiffness efficacy result is not robust when evaluated with certain sensitivity analyses; for example, there was no statically significant difference between treatment groups for this endpoint in the per-protocol population. It is also worth noting that the active comparator, prednisone IR, had virtually no effect on morning stiffness, which is somewhat surprising when compared to the placebo effect observed in Trial 007. While cross-study comparison has its limitation, this observation combined with the other factors puts the sensitivity of the assay and the reliability of the blinding into question. In terms of other endpoints, Trial 003 was not designed to show the superiority of NP01 over prednisone IR for the general treatment of RA. The reported results for the relative change in DAS28 (NP01 vs. prednisone IR, -9% vs. -12%) and the post-hoc ACR20 response rates (15% vs. 17%) at 12 weeks were numerically unfavorable for NP01.

Other secondary endpoints

(b) (4)

Efficacy conclusions

The results of Trial 007 support the efficacy of NP01 for the treatment of RA and are consistent with the known efficacy profile for prednisone IR. The data do not suggest any clinically important differences between NP01 and prednisone IR in terms of efficacy. The Clinical Review and Biostatistics Review have concluded that (b) (4)

The CDTL review concurs with this assessment.

7. Safety

Overview of safety database
The safety of NP01 is primarily supported by the established safety profile for immediate-release prednisone. The Applicant has provided additional safety information from the placebo-controlled controlled Trial 007 and the active-controlled Trial 003 with its open-label extension period. The study design for Trial 007 is described in the preceding section. The study design and assessment schedule for the double-blind phase of Trial 003 was similar, with the exception of prednisone IR as an active control rather than placebo. While a safety comparison between NP01 and prednisone IR is of clinical interest, the safety data from this trial are interpreted with the caveat that financial disclosure information was not provided and investigator bias in the reporting of adverse events remains a possibility. In addition, the duration of the double-blind comparison was relatively short (12 weeks) and involved fairly low doses of prednisone, with the majority of patients taking ≤5 mg NP01.

Safety data from the double-blind phases of the two trials were reviewed separately and pooled together as provided by the Applicant. The results were found to be similar regardless of the pooling strategy. Open-label data were reviewed separately.

Deaths and serious adverse events
The majority of the serious adverse events, including deaths, were the type of events (e.g., chest pain, myocardial ischemia/infarctions, injuries due to falls, orthopedic surgery, etc…) expected to occur in an older population with long-standing RA with other common comorbid conditions. One death was reported in the controlled trials, a fatal case of myocardial infarction in a patient assigned to prednisone IR in Trial 003. In terms of other SAEs, the overall numbers were similarly low across the treatment groups and were comprised of 1 or 2 cases per preferred term.

Adverse events of interest
In general, the nature of the adverse events observed in these trials was consistent with the historical clinical experience with low-dose corticosteroid therapy and the safety profile described in the current prednisone and prednisolone labels. The application included analyses of the following adverse events of interest: infections, gastrointestinal (upper abdominal pain, dyspepsia, abdominal discomfort, and abdominal pain), cardiovascular (hypertension and secondary hypertension), sleep disorders (insomnia and sleep disorder), metabolic (weight increased, blood glucose increased, occult blood positive, diabetes mellitus and glycosuria), central nervous system(CNS) (depression and delirium) and eye problems (cataracts and glaucoma). In Trial 003, overall rates between prednisone IR and NP01 were similarly low, including the rates for GI-related AEs such as upper abdominal pain and dyspepsia. While the strength of these findings is limited by the issues previously outlined for this trial as well as the relatively limited sample size, the results are reassuring in the sense that there do not appear to be any major clinical differences in terms of safety between NP01 and prednisone IR.

Common adverse events

As noted in the preceding section, the safety profile of NP01 was consistent with the known safety profile of prednisone IR. The most common AEs observed in Trial 007 occurring at a rate >1% and exceeding placebo included the following:

Table 4 Trial 007: Common adverse events occurring at a rate >2% and exceeding placebo

Preferred term	NP01 N=231 N, %	Placebo N=119 N, %
Patients with any AE	99 (43)	58 (49)
Nasopharyngitis	11 (5)	4 (3)
Hypertension	5 (2)	1 (1)
Diarrhea	4 (2)	1 (1)
Back pain	3 (1)	1 (1)
Vomiting	2 (1)	1 (1)

Source: Table 74, Clinical study report NP01-007

Safety conclusions

The safety profile for NP01 appears to be generally consistent with the established safety profile for prednisone IR described in the current product label. The clinical trial data do not indicate any clinically important differences in terms of safety. The Clinical Review has recommended that the NP01 label include the same safety information described in the prednisone IR label, noting that the NP01 trial data may underestimate the rate of AEs given the relatively low doses and short duration of treatment and be potentially misleading if included in the label. The CDTL review concurs with this assessment.

8. Advisory Committee Meeting/Regulatory Briefing

As prednisone is a well-known pharmaceutical entity and the proposed indication was not novel, an advisory committee meeting was not convened for this application. However, a Regulatory Briefing was held on May 18, 2012 to discuss possible regulatory pathways for approval and labeling. The Division summarized the application, noting that the CMC and clinical pharmacology data were sufficient to support approval for NP01 for a general RA treatment indication and that the clinical trial data did not demonstrate a clinically meaningful advantage for NP01 over prednisone IR. Specifically, the Division requested input from the panel on two possible options:

1. Approve NP01 for all of the same indications currently approved for prednisone IR and with labeling that matches the currently approved label for prednisone IR. Clinical pharmacology data relevant to NP01 would be included but no new clinical trial data would be presented. This approach would ensure that there was no implied advantage for NP01 over prednisone IR where none had been demonstrated.
2. Approve NP01 for a unique RA treatment indication, including new clinical data (ACR20 response rates from Trial 007) in the label. The inclusion of morning stiffness (b) (4) would be a review issue. This approach would maintain consistency with previous recommendations, (b) (5)

(b) (5)

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In addition, the Division sought feedback on the requirement for pediatric studies in the context of these two options.

Based on the presentations, the panel generally agreed that CMC and clinical pharmacology data would be sufficient to support NP01'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 secondary claims were approved for the product.

A follow-up meeting to the regulatory briefing was held with the Director of the Office of New Drugs (OND), the Deputy Center Director for Clinical Science, and the review division on July 3, 2012. The strength of the CMC and clinical pharmacology data and the limitations of the clinical data were discussed. Participants in the meeting agreed that the clinical trial data did not support the addition of new efficacy or safety claims and were not required to support approval of the application. The group considered what information warranted inclusion in the label and advised the review division that a label that maintained consistency with the approved labeling for immediate-release prednisone was most appropriate, including labeling for the broad range of indications. (b) (5)

. The meeting participants concluded that inclusion of limited clinical trial data based on the primary endpoint would be acceptable, provided that these data were balanced by disclaimer language that stated that a benefit for NP01 compared to prednisone IR in terms of efficacy or safety had not been established.

3. Pediatrics

As a new dosage form, NP01 triggers pediatric studies as required under the Pediatric Research Equity Act. (b) (4)

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However, based on the information in the NDA, the review team concluded that the pediatric requirements were already fulfilled and recommended that NP01 be labeled for all the indications and full age range approved for the reference product, prednisone IR. This

proposal was discussed with the Pediatric Research Committee on June 27, 2012, who concurred with the Division's assessment.

4. Other Relevant Regulatory Issues

The Applicant has provided the necessary financial disclosure information and certification of Good Clinical Practices for the placebo-controlled trial, Trial 007. As noted previously, the required financial disclosure information was not provided for the active-controlled, Trial 003. Therefore, this trial is considered inadequate for providing the basis for a regulatory decision and is viewed only as secondary support for safety.

(b) (4)

the review team has concluded that the CMC and clinical pharmacology data are sufficient to support a recommendation for approval and that the clinical trial data are not needed to support the general RA indication or the other indications already approved for immediate-release prednisone. The CDTL review agrees with this assessment.

5. Labeling

This section provides a high level overview of labeling, which remains pending at the time of this memorandum. The proposed tradename is Rayos, which has been found acceptable by the Division of Medical Error Prevention and Analysis (DMEPA). Consults from OPDP and OSE were received and included in the labeling process. Carton and container labeling were also reviewed. The following are summary comments regarding the package insert:

- The label for NP01 is in PLR format, in contrast to the reference product, PredniSONE. The label for NP01 will therefore maintain the content of the reference label but will follow a format similar to the PLR label for Flo-Pred (prednisolone oral suspension; NDA 22-067), including all class-wide labeling for Section 5, Warnings and Precautions.
- The indications statement for RA and other indications will be revised to maintain consistency with the Flo-Pred label.
- Relevant CMC and clinical pharmacology sections will be updated with information specific to NP01.
- Whereas the reference product is currently rated Pregnancy Category C, a recent review of possible teratogenic and fetotoxic effects resulted in the rating of prednisolone as Pregnancy Category D. NP01 will be similarly labeled Pregnancy Category D. It is expected that other prednisone labels will be similarly updated in the future.
- Limited clinical trial data relevant to the primary endpoint based and the general RA treatment indication may be included for the sake of description. It is noted that these data are not necessary for safe and appropriate use of the product. (b) (4). In addition, disclaimer language stating that the efficacy and safety profile of NP01 compared to prednisone IR has not been established.

6. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action is Approval pending agreed-upon labeling.

- Risk Benefit Assessment

The CMC and clinical pharmacology data submitted in the application support the reference to the well-established efficacy and safety of prednisone for the treatment of RA and other indications. The submitted clinical data from Trial 007, while not required, provides additional confirmation of efficacy and safety for the treatment of RA, (b) (4)

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

No postmarketing risk evaluation and management strategies are recommended.

The Applicant originally proposed a REMS comprised of a Medication Guide and Communication Plan to address safe use of NP01, including the timing of administration and the need for administration with food. Upon review, the review team has concluded that a REMS is not warranted and that standard labeling will be adequate to convey this information.

- Recommendation for other Postmarketing Requirements and Commitments

No postmarketing requirements or commitments are recommended.

- Recommended Comments to Applicant

There are no additional comments.

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/s/

SUSAN L LIMB
07/05/2012