HORIZON PHARMA

September 3, 2013

2013 SEP -4 P 12:11

BY COURIER

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, Maryland 20852

RE: Bioequivalence for ANDAs Referencing NDA No. 202020 for RAYOS® (prednisone) Delayed-Release Tablets

Dear Sir or Madam:

CITIZEN PETITION

Horizon Pharma, Inc. ("Horizon") submits this Citizen Petition in accordance with the Food and Drug Administration's ("FDA's" or the "Agency's") regulations set forth in 21 CFR § 10.30. Horizon requests that the Commissioner of Food and Drugs take the actions described below with respect to any Abbreviated New Drug Application ("ANDA") submitted to FDA and listing RAYOS® (prednisone) delayed-release tablets 1 mg, 2 mg, or 5 mg ("RAYOS® tablets") as the reference listed drug ("RLD"). RAYOS® tablets are approved for use in the treatment of various disease and conditions, including numerous rheumatologic conditions including *inter alia* rheumatoid arthritis.

As discussed in greater detail herein, RAYOS® tablets were developed to address the circadian nature of signs and symptoms associated with inflammatory diseases such as rheumatoid arthritis ("RA"). Specifically, RAYOS® tablets employ a unique delayed-release mechanism that results in release of prednisone in the early morning just as clinical symptoms of the inflammatory disease are particularly evident. This delayed release mechanism results in two significant pharmacokinetic ("PK") features that impact the drug's overall pharmacodynamic ("PD") effect and which distinguishes it from immediate-release prednisone. First, RAYOS® tablets delay the release of prednisone until four hours after it is ingested. This mechanism allows patients the convenience of taking RAYOS® tablets shortly before bedtime, with the benefit of release of prednisone in the early morning hours when pro-inflammatory cytokines associated with signs and symptoms of inflammatory diseases are on the rise. Second, the delayed-release mechanism of the RAYOS® tablets results in a significant food effect, which is not seen in immediate release prednisone products. As a result, RAYOS® tablets must be taken with food to insure appropriate bioavailability ("BA").

A generic product that uses a delayed release mechanism other than that employed by the RAYOS® tablets (e.g., an enteric coating) likely would have a different PK profile as compared

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to RAYOS® tablets, due to sensitivity to fluctuations in pH and gastric emptying rate. Because RAYOS® tablets are specifically formulated to deliver prednisone at a certain time relative to increases in pro-inflammatory cytokines, this could have an impact on overall therapeutic effect. Furthermore, use of a different mechanism for delayed-release may result in a product that does not exhibit the same food effect as the RAYOS® tablets. Therefore, FDA should not approve any ANDA for a generic version of RAYOS® tablets that uses a different delayed-release mechanism, unless such ANDA demonstrates bioequivalence ("BE") both in terms of delayed-release and BA after release, as demonstrated under fed conditions.

I. ACTIONS REQUESTED

Horizon therefore requests that, to establish BE for any ANDA that lists RAYOS® tablets as the RLD, as required by section 505(j)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), FDA require:

(1) data and information demonstrating both that the proposed generic product (a) does not begin to release the active substance (prednisone) until approximately four hours after intake (i.e., has an equivalent lag time and T_{max}), and (b) has an equivalent BA profile to RAYOS® after t=4 hours; and

(2) such data and information be obtained under fed conditions.

II. STATEMENT OF GROUNDS

A. Factual Background

1. *Prednisone in the Treatment of RA*

Corticosteroids were first used to successfully treat RA in the late 1940s and are now used to treat a wide range of diseases associated with an inflammatory component. Oral, immediate-release prednisone was approved by FDA in 1955 for multiple types of inflammatory arthritis and other inflammatory, non-rheumatologic conditions. Immediate-release prednisone tablets also are indicated as adjunctive therapy for short-term administration or low dose maintenance therapy of RA including juvenile rheumatoid arthritis (juvenile inflammatory arthritis), and various other diseases.

The progression of RA and other inflammatory diseases is characterized by a circadian rhythm of pro-inflammatory cytokines. This often results in particularly severe signs and symptoms of disease in the morning hours. Patients with active RA suffer from clinical signs and symptoms that include joint stiffness, pain, and swelling. Clinical symptoms vary during the day and are more severe early in the morning after awakening than in the afternoon or evening. Indeed, morning stiffness is a prominent symptom of RA.[1]

[1] Cutolo, M., 2012. Chronobiology and the Treatment of Rheumatoid Arthritis. Curr Opin Rheumatol. 24:312-318.

The mechanisms responsible for the circadian variation of RA symptoms are complex and involve the hypothalamic-pituitary-adrenal ("HPA") axis and the elaboration of various endogenous inflammatory mediators. Inflammation causes increased production of inflammatory cytokines. In comparison with healthy subjects, RA patients have higher serum concentrations of interleukins ("IL"), especially IL-6. Importantly, those levels display a pronounced circadian rhythm, with higher early morning concentrations that peak at 02:00 a.m. to 06:00 a.m.[2]

Typical morning administration of immediate-release prednisone may not optimally address this circadian rhythm for RA. This is because immediate-release prednisone tablets, taken when the patient awakens in the morning, often do not release therapeutic amounts of prednisone until significantly after pro-inflammatory cytokines have reached their peak.[3] Research suggests, however, that low-dose glucocorticoid therapy such as prednisone for RA and certain other diseases, such as asthma, and polymyalgia rheumatica ("PMR") can be optimized by addressing the circadian rhythms of the pathophysiologic mechanisms and symptoms of the disease.[1] A release profile that allows for convenient dosing times while still releasing prednisone in tandem with early morning elevation of pro-inflammatory cytokines may more effectively address morning symptoms of RA.

The RAYOS® product was developed to provide just such a release profile. Specifically, the RAYOS® product was developed as a delayed-release prednisone formulation to provide a shift of the concentration time curve of immediate-release prednisone by about 4 hours. This shift is intended to allow for convenient dosing, accompanied by release of prednisone in synchronization with the circadian rhythm. Thus, RAYOS® tablets can be taken once daily at bedtime. Given the four-hour delay in release of prednisone, anti-inflammatory prednisone blood levels are achieved in the early-morning hours, just as early-morning flare-up of pro-inflammatory cytokines and clinical symptoms takes place. By synchronizing the release of daily prednisone with the early morning release of cytokines, RAYOS® tablets reduce the signs and symptoms of RA while also achieving a significant decrease in critical morning symptoms of RA. For example, in clinical trials, patients taking RAYOS® tablets at bedtime suffered from morning stiffness on average for only 46 minutes, as compared to 85 minutes for the control group.[4]

2. *RAYOS®*

FDA approved RAYOS® tablets on July 26, 2012 under New Drug Application ("NDA") No. 202020 pursuant to FD&C Act § 505(b)(2). The approved label for RAYOS® tablets includes the same indications currently approved for immediate-release prednisone, i.e.:

[2] Kirwan, J., Clarke, L., Hunt, L., Perry, M., Straub, R., Jessop, D., 2010. Effect of Novel Therapeutic Glucocorticoids on Circadian Rhythms of Hormones and Cytokines in Rheumatoid Arthritis. Ann. N.Y. Acad. Sci. 1193:127 – 133.

[3] Arvidson, N., Gudbjörnsson, B., Larsson, A., Hällgren, R., 1997. The Timing of Glucocorticoid Administration in Rheumatoid Arthritis. Annals of Rheumatic Diseases. 56:27 – 31.

[4] *See* RAYOS® PI, Section 14.

- as an anti-inflammatory or immunosuppressive agent for certain allergic, dermatologic, gastrointestinal, hematologic, ophthalmologic, nervous system, renal, respiratory, rheumatologic, specific infectious diseases or conditions and organ transplantation;
- for the treatment of certain endocrine conditions; and
- for palliation of certain neoplastic conditions.

In contrast to the label for immediate-release prednisone, the RAYOS® label includes clinical pharmacology data recommending that the delayed exposure characteristics be taken into consideration so that RAYOS® tablets are not used in conditions where the delayed-release characteristics would be undesirable. The RAYOS® label also describes clinical studies wherein RAYOS® tablets were administered at 10 pm.

B. Applicable Law

Under the FD&C Act and FDA's implementing regulations, in order for FDA to approve an ANDA, the sponsor must demonstrate, among other things that its proposed generic drug product is bioequivalent to the RLD. *See* FD&C Act § 505(j)(2)(A)(iv); 21 C.F.R. §§ 314.127(a)(7) and 314.127(a)(6)(i). FDA's general recommendation for BE testing of modified-release, orally administered and systemically absorbed drug products is a single-dose fasting study and a single-dose food-effect study. *See Bioavailability and Bioequivalence for Orally Administered Drug Products – General Considerations* (BA/BE Guidance) at page 16. *See also, Food-Effect Bioavailability and Fed Bioequivalence Studies*, December 2002, at page 4. For two orally administered drug products to be bioequivalent, the active drug ingredient or active moiety in the test product must exhibit the same rate and extent of absorption as the reference drug product. *See* 21 CFR 320.1(e) and 320.23(b).

C. Discussion

1. *RAYOS® Has a Unique PK Profile That Contributes to Its Overall PD Effect*

The PK properties of immediate-release prednisone are well known and generally apply to RAYOS® tablets. However, because RAYOS® tablets employ a delayed-release mechanism,

> [t]here are two characteristics that are unique for RAYOS®. First, RAYOS® has a pronounced food effect that is not present for immediate-release prednisone. Second, RAYOS® has a delayed T_{max} compared to immediate-release prednisone.[5]

These two unique characteristics differentiate RAYOS® tablets from immediate-release prednisone and, potentially, from other delayed-release formulations.

[5] Summary Review, Center for Drug Evaluation and Research Application Number: 202020Orig1s000, review completion date July 25, 2012, at page 4.

First, the delayed T_{max} of RAYOS® tablets, as illustrated in Figure 1, is a key difference between RAYOS® tablets and immediate-release prednisone:

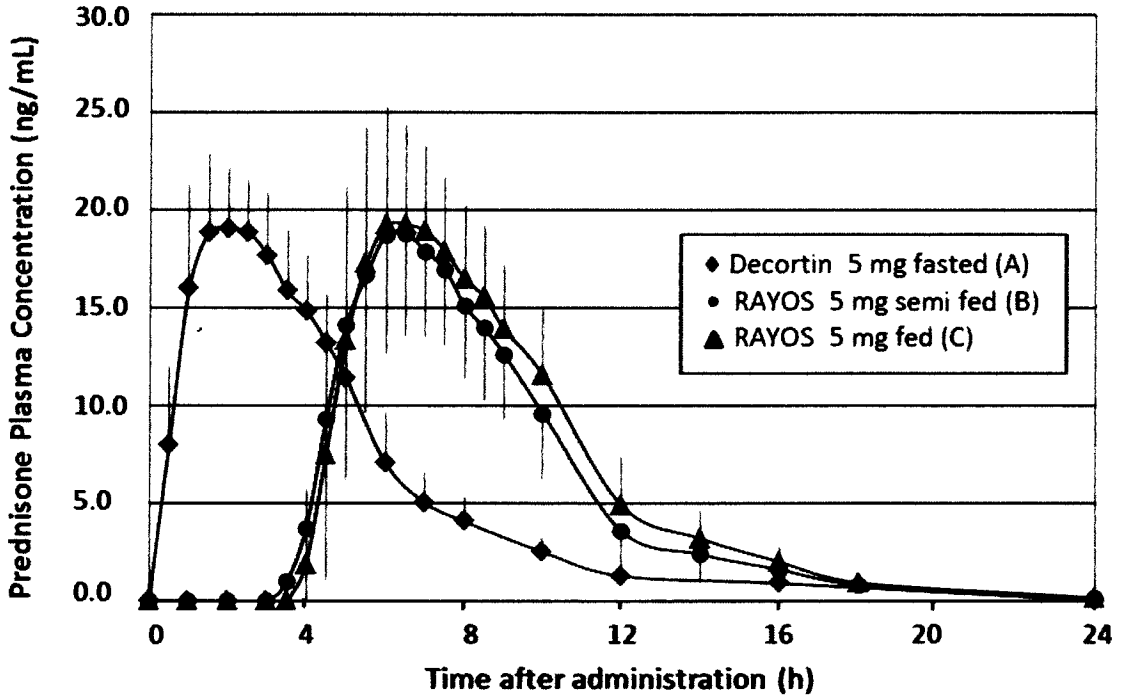

Figure 1. Mean plasma levels of prednisone after a single dose of 5 mg prednisone administered as a 5 mg RAYOS® (prednisone) delayed-release tablet or a 5 mg prednisone immediate release tablet. [A: 5 mg IR tablet under fasting condition, administered at 2 am; B: 5 mg RAYOS® tablet administered 2.5 hours after a light evening meal; and C: 5 mg RAYOS® tablet administered immediately after dinner.]

The RAYOS® tablets four-hour delayed burst-release profile is achieved by enclosing a tablet core containing immediate-release prednisone within a release controlling shell. Drug release is triggered by penetration of water. After a delay or lag time (specifically engineered to four hours), the outer tablet shell opens into two halves, exposing the prednisone core. From this point forward, the core tablet releases the prednisone active drug substance in a manner that is similar to an immediate-release tablet. Critically, the delayed-release mechanism employed by the RAYOS® tablets is completely independent of pH.[6] In other words, RAYOS® tablets begin to release prednisone after a lag time of t=4 hours regardless of the physiological pH environment in the gastrointestinal tract or by excipients that might alter the pH microclimate.

The unique delayed-release profile of RAYOS® tablets makes an important contribution to the drug's overall PD profile and therapeutic effect. If RAYOS® tablets are taken at bedtime, release of prednisone is delayed until the early morning hours. This synchronizes the increase in

[6] Charman, W., Porter, C., Mathani, S., Dressman, J., 1997. Physicochemical and Physiological Mechanisms for the Effects of Food on Drug Absorption: The Role of Lipids and pH, Journal of Pharmaceutical Sciences, 86 (3): 269 – 282.

anti-inflammatory prednisone blood levels with early morning flare-up of pro-inflammatory cytokines and clinical symptoms as illustrated in Figure 2.[2,7]

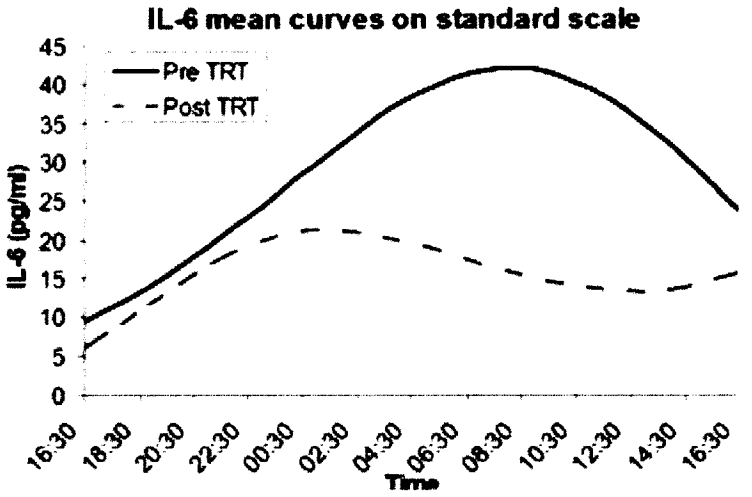

Figure 2. Plasma IL-6 levels in nine patients with RA before and after 2 weeks of treatment with modified-release prednisone 5 mg/day

In phase 3 clinical studies, RAYOS® tablets effectively reduced the signs and symptoms of rheumatoid arthritis. Importantly, however, it also demonstrated beneficial effects on morning stiffness, a symptom of RA that is not always effectively controlled by available treatments. The RAYOS® tablets Prescribing Information ("PI") includes data from those clinical trials confirming this aspect of the efficacy of RAYOS® tablets:

> The percent change from baseline in the duration of morning stiffness at 12 weeks was assessed as a prespecified secondary endpoint. Patients treated with RAYOS® had a median decrease in the duration of morning stiffness of 55 % compared to 33 % in placebo-treated patients (20 % estimated median difference between treatment groups with 95% confidence interval [7, 32]). This corresponds to a median duration of morning stiffness of 46 minutes in the RAYOS® group and 85 minutes in the placebo group.

Second, FDA has observed that RAYOS® tablets have a "pronounced" and "substantial"[8] food effect as demonstrated by a 60% decrease in its BA in fasting subjects."[9] As demonstrated in Figure 3, and as noted in FDA's clinical review of RAYOS® tablets, "[a]dministration of

[7] See, Section 2.1 of the PI for RAYOS which states that "The maximal activity of the adrenal cortex is between 2 am and 8 am and is minimal between 4 pm and midnight. Exogenous corticosteroids suppress adrenocorticoid activity the least when given at the time of maximal activity."
[8] Medical Review, Center for Drug Evaluation and Research Application Number: 202020Orig1s000, review completion date June 20, 2012, at page 18.
[9] Clinical Pharmacology and Biopharmaceutics Review(s), Center for Drug Evaluation and Research Application Number: 202020Orig1s000, review submission date September 26, 2011, at page 3.

[RAYOS® tablets] under fasting conditions resulted in prolonged *in vivo* lag time and significantly lower and highly variable prednisone and prednisolone plasma concentrations compared to fed conditions (Study NP01-006)."[10]

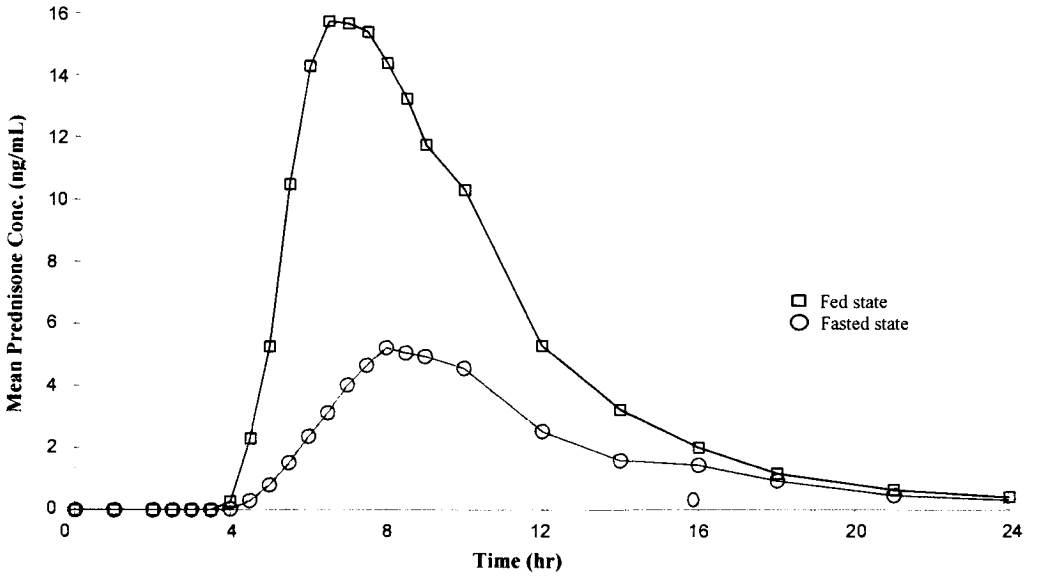

Figure 3. Effect of food on pharmacokinetics of RAYOS® Tablets

This food effect is a direct result of the particular delayed-release mechanism of the RAYOS® tablets and is not observed in immediate release prednisone. This can be explained through two well-understood principles. First, the presence of food in the stomach slows gastric emptying. Thus, any tablet or capsule that is swallowed with food will remain in the stomach for a longer period of time than it would be if taken in the fasted state. This effect is particularly pronounced when a drug is taken with a high fat meal. Second, most systemic drug absorption takes place in the stomach and the small intestine[11]. These facts are critical to the unique delayed-release profile of RAYOS® tablets. If RAYOS® tablets are taken in the fed state, the tablets spend considerably more time in the stomach than they would if taken in the fasted state. Thus, the RAYOS® tablets are still in the stomach/small intestines when the four-hour time point is reached and the outer shell breaks open. Because the RAYOS® tablets release profile is completely independent of environmental pH, what remains is essentially immediate-release prednisone, which is taken up into systemic absorption in much the same way that an immediate-release dose would. If, by contrast, RAYOS® tablets are taken in the fasted state, passage of the tablets through the stomach and small intestines occurs much more quickly. Again, RAYOS® tablets release prednisone after a lag time of t=4 hours regardless of environmental pH levels. Thus, if taken in a fasted state, the RAYOS® tablets will be farther down the digestive track at

[10] *Id.*

[11] Vogt, M., Derendorf, H., Krämer, J., Junginger, H.E., Midha, K.K., Shah, V.P., Stavchansky, S., Dressman, J.B., Barends, D.M., 2007. Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Prednisone, Journal of Pharmaceutical Sciences, 96 (6):1480 – 1489.

the four-hour point, where systemic absorption is less efficient. This explains the dramatic differences in the curves in Figure 3.

Thus, the particular mechanism that RAYOS® tablets use to achieve delayed-release results in a PK profile that is highly unique for a delayed-release product, namely a delayed-release drug whose PK profile upon release is nearly identical to immediate-release formulations. As FDA noted in its review of a relative BA study conducted with RAYOS® tablets and immediate release Decotrin tablets:

> Because of a significant food effect of the delayed-release formulation, the relative BA study was conducted with the delayed-release RAYOS® tablets given under semi-fasted or fed condition and the immediate-release reference tablets given under fasted condition. The exposures of prednisone from RAYOS® were comparable to those from immediate-release tablets under fasted condition. However, the T_{max} was delayed 4 hours for RAYOS® as compared to immediate-release tablets (Figure 1). The exposure of prednisone from immediate release tablets was not affected by the intake of food.[12]

As evident in clinical trial results and as acknowledged by FDA, the food effect and the four-hour delayed release make RAYOS® tablets a different product than immediate-release prednisone tablets. Those distinguishing factors are included in the RAYOS® tablets PI, which indicates that the PK profile of RAYOS® tablets has an approximately 4-hour lag time from that of immediate-release prednisone formulations. The RAYOS® tablets PI also mandates that RAYOS® tablets should be taken with food as administration under fasting conditions resulted in "significantly lower and highly variable prednisone and prednisolone [the active metabolite of prednisone] plasma concentrations compared to fed conditions."[13]

2. *A Generic Product That Uses a Different Delayed Release Mechanism Might Exhibit Significantly Different PK Properties and PD Effects*

An ANDA applicant seeking approval to market a generic copy of RAYOS® tablets, which employs a different delayed-release mechanism, might not display the same prednisone release profile or food effect of the RAYOS® tablets, the two features that FDA found to make RAYOS® tablets distinct from immediate-release prednisone. Instead the generic copy might exhibit significant differences in PK profiles from the RAYOS® tablets, which may have significant PD and therapeutic consequences.

For example, an ANDA product that used an enteric coating to achieve delayed-release likely would be unable to replicate the four-hour delayed burst-release profile of the RAYOS®

[12] Summary Review, Center for Drug Evaluation and Research Application Number: 202020Orig1s000, review completion date July 25, 2012, at page 4.
[13] Clinical Pharmacology and Biopharmaceutics Review(s), Center for Drug Evaluation and Research Application Number: 202020Orig1s000, review submission date September 26, 2011, at page 3.

tablets. This is because enteric coatings are, by their nature, subject to the vagaries of pH in the intestinal milieu[14]. As a result, there could be significant variability in the lag time and exposure of an enteric coated prednisone tablet as a result of differences in the timing of administration, presence of food in the gastrointestinal tract, type of that food, gastric emptying rate and other factors – all factors that alter environmental pH. In other words, the unique delayed-release mechanism of the RAYOS® tablets makes it immune to significant intra- and inter-subject variability. By contrast, an enterically coated prednisone product may be very much subject to these factors and, thus, unlikely to be able to consistently produce the four-hour delayed burst-release profile of the RAYOS® tablets.

The inability of a prednisone delayed-release product to consistently produce the four-hour delayed burst-release profile of the RAYOS® tablets could have significant consequences. As noted above, RAYOS® tablets are specifically designed to allow convenient dosing at bedtime while still resulting in release of prednisone in the early morning hours when pro-inflammatory cytokines are on the rise. A delayed-release prednisone product that does not consistently produce the same four-hour delayed-release profile might not be able to provide the therapeutic benefit of RAYOS® tablets with convenient bedtime dosing.

Similarly, a generic version of RAYOS® tablets that employs a different means of delaying release of prednisone, such as an enteric coating, might display a significantly different food effect or no food effect at all. Once again, release of prednisone by RAYOS® tablets is not impacted by changes in pH. Thus, the tendency of food to delay gastric emptying has a direct impact on systemic absorption of prednisone. By contrast, in the case of an enterically coated delayed release prednisone product, the presence or absence of food may be irrelevant depending on the pH levels present in the intestinal milieu at the time of ingestion. Such a product might therefore have an entirely different food effect than does RAYOS® tablets, or none at all.

3. *BE Testing of Proposed ANDAs for Generic versions or RAYOS® Should Guarantee the Presence of the Two Differentiating Features of RAYOS®*

Pursuant to section 505(j)(2)(A)(iv) of the FD&C Act, any ANDA that references RAYOS® tablets as the RLD must demonstrate that its proposed generic product is bioequivalent to RAYOS® tablets. In light of the discussion above, this showing of BE must demonstrate that such a proposed generic product maintains the two distinguishing features of RAYOS® tablets: the pronounced food effect and the 4-hour delayed T_{max} and associated burst-release profile. Thus, Horizon requests that the FDA take the following actions to ensure BE of a generic product.

First, not only should FDA ensure that BE criteria for C_{max} and AUC are met, but FDA should also require the ANDA applicant to demonstrate comparable lag time and T_{max} between RAYOS® tablets and the proposed generic product. Second, PK data should also demonstrate that once the generic prednisone release begins at t=4 hours, the proposed generic product releases its prednisone at the same rate and extent as does the RAYOS® tablets. In other words,

[14] Frey, B., Frey, F., 1990. Clinical Pharmacokinetics of Prednisone and Prednisolone, Clin. Pharmaockinet. 19 (2); 126 – 146.

the generic product's release profile must, like RAYOS® tablets, mirror that of an immediate release prednisone product after the four-hour delayed-release. As noted above, RAYOS® tablets are uniquely formulated to release the prednisone in the early morning hours just as pro-inflammatory cytokines are on the rise, while still offering convenient bedtime dosing. A proposed generic version of RAYOS® tablets that does not maintain this distinctive release profile would not provide the same balance of convenience and benefit.

Finally, and critically, because of the magnitude of the food effect and its potential impact on drug exposure, patient safety, and efficacy, Horizon urges FDA to require that BE between RAYOS® tablets and any generic prednisone be demonstrated under fed conditions. As noted above, the fact that RAYOS® tablets are not dependent on the pH environment at the time of RAYOS® tablets ingestion directly causes RAYOS® tablets to demonstrate a significant food effect not seen in immediate-release products. A product that used a different method for achieving delayed-release, such as an enteric coating, likely would be pH dependent. Thus, fed BE testing is critical to ensuring that the generic product is bioequivalent to RAYOS® tablets and bears the two features that FDA noted in its review distinguish RAYOS® tablets from immediate release prednisone.[15] More importantly, failure to do so could compromise the therapeutic efficacy of the product when taken before bedtime, as intended.

III. ENVIRONMENTAL IMPACT

Horizon claims a categorical exclusion under 21 C.F.R. § 25.31.

IV. ECONOMIC IMPACT STATEMENT

Horizon will, upon request by the Commissioner, submit economic impact information, in accordance with 21 C.F.R. § 10.30(b).

[15] Moreover, to require BE studies under fed conditions is consistent with current recommendations provided by FDA in a December 2002 guidance for industry, titled "Food-Effect Bioavailability and Fed Bioequivalence Studies. That guidance states that "In addition to a BE study under fasting conditions, a BE study under fed conditions should be conducted for **all orally administered modified release** drug products." FDA explained in that guidance that those studies under fed conditions are required because, "[F]or **all modified-release drug products**, food effects are most likely to result from a more complex combination of factors that influence the in vivo dissolution of the drug product and/or the absorption of the drug substance. In these cases, the relative direction and magnitude of food effects . . . and the effects on the demonstration of [bioequivalence] are **difficult, if not impossible, to predict** without conducting a fed [bioequivalence] study." Guidance for Industry, Food-Effect Bioavailability and Fed Bioequivalence Studies, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), December 2002, at page 2.

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V. CERTIFICATIONS

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to Horizon which are unfavorable to the Petition.

Horizon makes the following certification pursuant to FDC Act § 505(q)(1)(I):

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. Horizon's current understanding of the food effect associated with RAYOS is based on clinical studies completed between February 2008 and April 2010 assessing RAYOS in fed versus fasted states. Horizon came to a more complete understanding of the effect that Horizon's distinguishing features have on PD in late 2012/early 2013. Horizon became aware of the potential for ANDA applicants to use enteric coating as a method for achieving delayed release in a generic prednisone product in approximately March 2013. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive these payments from the following persons or organizations: I am a paid employee of Horizon and submit this citizen petition in that capacity. I do not expect to receive any additional compensation for filing this petition on Horizon's behalf. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Timothy P. Walbert

Timothy P. Walbert
Chairman, President and Chief Executive Officer

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