DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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MAR 12 2014

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

Re: Docket No. FDA-2013-P-1283

Dear Mr. Walbert:

This responds to your citizen petition received on October 17, 2013 (Petition), requesting that the Food and Drug Administration (FDA or the Agency) not approve any abbreviated new drug applications (ANDAs) for generic[1] versions of Rayos (prednisone) delayed-release tablets, 1 milligram (mg), 2 mg, or 5 mg (Rayos), unless the ANDA applicant meets certain conditions. Specifically, you request that FDA require ANDA applicants to submit data and information demonstrating that the proposed generic product:

- does not begin to release the active substance (prednisone) until approximately 4 hours after intake (i.e., has an equivalent lag time and T_{max}),[2] and
- has an equivalent bioavailability profile to Rayos after t=4 hours.

You also request that FDA require ANDA applicants to obtain such data and information under fed conditions.

FDA has carefully considered the information submitted in the Petition and other relevant data available to the Agency. Based on our review of these materials and for the reasons described below, your Petition is granted in part and denied in part.

I. Background

A. Rayos

FDA approved the Horizon Pharma, Inc. (Horizon) new drug application (NDA 202020) for Rayos on July 26, 2012. Horizon submitted the NDA for Rayos under section 505(b)(2) of the

[1] *Generic* is not defined in the Federal Food, Drug, & Cosmetic Act (FD&C Act) or in FDA regulations. As used in this response, the term *generic drug* refers to a new drug product for which approval is sought in an ANDA submitted under section 505(j) of the FD&C Act (21 U.S.C. 355(j)).

[2] T_{max} is defined as the time required to reach the peak drug concentration after administration.

Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355 (b)(2)).[3] Rayos is a delayed-release tablet available in 1-mg, 2-mg, or 5-mg dosage strengths and is indicated:

- 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.

Unlike the labeling for the immediate-release prednisone product, the labeling for Rayos includes clinical pharmacology data recommending that administration should take into account the delayed-release pharmacokinetics characteristics and the disease or condition being treated.[4] The labeling also describes clinical studies where Rayos tablets were administered at 10 p.m., but does not give any specific bedtime dosing recommendations.[5]

B. Legal and Regulatory Background

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the FD&C Act (21 U.S.C. 355(j)), which established the current ANDA approval process. To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the reference listed drug (RLD)[6] is safe and effective. To rely on a previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the FD&C Act). In addition, an ANDA must contain (with certain exceptions not relevant here) information to show that the proposed drug has the same active ingredient(s), indications for use, route of administration, dosage form, strength, and labeling as the RLD (section 505(j)(2)(A) of the FD&C Act). FDA must approve an ANDA unless the information submitted in the ANDA is insufficient to meet the requirements delineated in section

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[3] Section 505(b)(2) of the FD&C Act provides that an application may be submitted under section 505(b)(1) for a drug for which the safety and effectiveness investigations relied upon by the applicant to support approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

[4] See DOSAGE AND ADMINISTRATION (section 2) of the Rayos labeling.

[5] See CLINICAL STUDIES (section 14) of the Rayos labeling.

[6] A reference listed drug (or RLD) is defined in 21 CFR 314.3 as "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application." Section 314.3 further defines a "listed drug" as "a new drug product that has an effective approval under section 505(c) of the [FD&C] act for safety and effectiveness or under section 505(j) of the [FD&C] act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the [FD&C] act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness." RLDs are identified in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations*, generally known as "the Orange Book."

505(j)(2)(A), including a demonstration of bioequivalence (section 505(j)(4) of the FD&C Act). The basic assumption underlying the Hatch-Waxman Amendments is that bioequivalent drug products that meet certain criteria are therapeutically equivalent and may be substituted for each other.[7] The general criteria for therapeutic equivalence include the following: the products (1) contain identical amounts of the same active ingredient(s) in the same route of administration and dosage form; (2) meet applicable standards of strength, quality, purity, and identity; (3) are manufactured in compliance with current good manufacturing practices regulations; and (4) are adequately labeled.[8]

FDA regulations at 21 CFR part 320 list acceptable methodologies for determining the bioequivalence of drug products. These methodologies include pharmacokinetic (PK) studies, pharmacodynamic (PD) studies, comparative clinical trials, and in vitro studies. The selection of the method used depends on the purpose of the study, the analytical methods available, and the characteristics of the drug product under consideration (§ 320.24). The courts have expressly upheld FDA's regulatory implementation of the FD&C Act's bioequivalence requirements (see, e.g., *Schering Corp. v. FDA*, 51 F.3d 390, 397-400 (3d Cir. 1995); *Sanofi-Aventis v. FDA*, 842 F.Supp.2d 195, 214 (D.D.C. 2012); *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994)).

FDA's general recommendation for bioequivalence testing of modified-release, orally administered, and systemically absorbed drug products is a single-dose fasting study and a single-dose food-effect study.[9] FDA recommends administration of single doses of the test and reference drug products to subjects during the respective treatment phases, with measurement of the plasma concentrations of the test and reference drugs over time.

To evaluate the rate and extent of test drug absorption, the measured plasma concentrations for each subject should be plotted against time of measurement with the plasma sampling time on the horizontal (x) axis and corresponding plasma drug concentration on the vertical (y) axis. The relevant PK parameters calculated from these data include the area under the concentration-time curve (AUC), calculated to the last measured concentration time (AUC_{0-t}) and extrapolated to infinity (AUC_{∞}). This parameter represents the *extent* of absorption (i.e., how much of the drug in the given dose was absorbed). The other relevant PK parameters are the maximum or *peak* drug concentration (C_{max}) and the time required to reach the peak drug concentration after administration (T_{max}), which reflect the rate of absorption. FDA recognizes that, under certain circumstances, it may be appropriate to use a partial AUC parameter to ensure comparable therapeutic effects.

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[7] See section 505(j) of the FD&C Act.

[8] See the Orange Book, 33rd ed., at vii.

[9] See the FDA guidance for industry *Bioavailability and Bioequivalence for Orally Administered Drug Products – General Considerations* (March 2003); see also the draft guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (December 2013) (available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm).

FDA considers products bioequivalent when the 90 percent confidence intervals for the test/reference PK parameter are entirely within an 80 to 125 percent acceptance interval.[10] The choice of the 80 to 125 percent acceptance interval reflects decades of scientific data on the variability of product characteristics (such as potency) within and between batches, as well as biological variability in patients. From these data, FDA concluded that the variability in PK values allowed under this acceptance interval would not adversely affect clinical outcomes, because this variability is within the range of differences that can arise from other product-specific and biological factors.[11]

C. FDA's Bioequivalence Recommendations for Prednisone (Delayed-Release Tablets/Oral)

FDA's *Draft Guidance on Prednisone*[12] delayed-release tablets/oral (Prednisone Bioequivalence Guidance) provides recommendations on how to design bioequivalence studies to support ANDAs for these prednisone products. The Agency recommends the following:

- Single-dose, fasting, two-way crossover in vivo comparing the 5-mg strength test product to the RLD, Rayos.
- Single-dose, fed, two-way crossover in vivo comparing the 5-mg strength test product to the RLD, Rayos.

Bioequivalence should be demonstrated based on a 90 percent confidence interval. If the bioequivalence study utilizing the 5-mg strength is successful, in vivo studies using the 1mg and 2-mg strengths may be waived if certain criteria are met.

II. Discussion

Your petition describes the history of the use of corticosteroids in the treatment of rheumatoid arthritis (RA) (Petition at 2). Starting in the 1940s, corticosteroids were being used to treat RA. In 1955, FDA approved an oral, immediate-release prednisone product to treat inflammatory diseases, such as RA. You describe the signs and symptoms of RA that include joint stiffness, pain, and swelling and state that the clinical symptoms can vary during the day, but tend to be more severe in the morning after awakening (Petition at 2). You state that the circadian variation of RA symptoms is complex and that typical morning administration of immediate-release prednisone may not optimally address this circadian rhythm for RA (Petition at 3). You claim that the Rayos delayed-release tablet, which releases prednisone 4 hours after ingestion, was

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[10] See the FDA guidance for industry *Statistical Approaches to Establishing Bioequivalence* (available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm).

[11] Dighe SV, and WP Adams, 1991, Bioequivalence: A United States Regulatory Perspective. In: PG Welling, LS Tse, and S Dighe, eds., Pharmaceutical Bioequivalence, Marcel Dekker, Inc., New York, 347-380.

[12] The draft guidance, when finalized, will represent FDA's current thinking on this topic (available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm).

developed to specifically address the circadian nature of signs and symptoms associated with inflammatory diseases, such as RA (Petition at 1). The 4-hour delayed-release mechanism allows patients to take Rayos shortly before bedtime so that the release of the prednisone will coincide with the morning hours. You suggest that the Rayos delayed-release mechanism results in PK features that have an impact on the drug's PD effect, making Rayos different from an immediate-release prednisone product (Petition at 1, 2-3). You also argue that the delayed-release mechanism of Rayos results in a significant food effect whereby Rayos must be taken with food to insure appropriate bioavailability (Petition at 1, 7). These claims and arguments are addressed below.

A. Pharmacokinetic Profile and Therapeutic Effect

As mentioned above, the Rayos labeling contains the same indications as the immediate-release form of prednisone, but your petition highlights the fact that the Rayos labeling 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 (Petition at 4). The labeling also describes clinical studies where Rayos tablets were administered at 10 p.m. You claim that Rayos was developed with a special release profile to allow for a convenient dosing time (bedtime) and a release of the drug in the early morning hours to coincide with the morning symptoms of RA (Petition at 3). You argue that the unique delayed-release profile of Rayos makes an important contribution to the overall PD profile and therapeutic effect because synchronizing the release of the drug product with the early morning symptoms of RA reduces the daily signs and symptoms of the disease (Petition at 5-6). In essence, you argue that the special release mechanism optimizes the treatment of RA.

We disagree with your assessment that the release mechanism of Rayos provides a therapeutic effect that makes it more special or unique than an immediate-release prednisone product. Although the release mechanism may provide dosing convenience, it does not necessarily optimize the treatment of RA.

Rayos is designed to release prednisone during the middle of the night following bedtime dosing to shift the concentration time curve of immediate-release prednisone by about 4 hours. The rationale for this design was based on chronotherapy for morning stiffness in RA patients. Although the approved Rayos drug label states that "Patients treated with Rayos had a median decrease in the duration of morning stiffness of 55% compared to 33% in placebo-treated patients (20 minute estimated median difference between treatment groups with 95% confidence interval),"[13] it should be noted that the comparison was made between Rayos and a placebo. In addition, there are no conclusive clinical trials comparing Rayos with the immediate-release formulation on the relief of morning stiffness. Although the drug label states that "[t]he timing of RAYOS administration should take into account the delayed-release pharmacokinetics and the disease or condition being treated,"[14] it does not specifically state that the product should be

[13] See CLINICAL STUDIES (section 14) of the Rayos labeling.

[14] See DOSAGE AND ADMINISTRATION (section 2) of the Rayos labeling.

administered at bedtime. It is important to note that the Rayos labeling does not contain any claim or data that the timing of dosing results in improved morning stiffness. Furthermore, it is well established that prednisone is an effective treatment for RA and any anti-inflammatory treatment that positively affects RA would be expected to improve morning stiffness, in addition to improving the other signs and symptoms of RA.

B. Delayed-Release Mechanism

You state that the 4-hour delayed burst-release profile is achieved by enclosing a tablet core containing immediate-release prednisone within a release controlling shell (Petition at 5). As a result, the delayed-release profile of Rayos makes an important contribution to the drug's overall PD profile and therapeutic effect (Petition at 5). According to you, a generic product that uses a different delayed-release mechanism (e.g., enteric coating) might exhibit significantly different PK properties and PD effects (Petition at 8). Additionally, you claim that Rayos is not impacted by changes in pH because of its unique delayed-release mechanism, but other mechanisms (enteric coating) are subject to changes in pH in the intestinal tract (Petition at 9). You suggest that an ANDA applicant that uses a different delayed-release mechanism might not display the same prednisone release profile or food effect of the Rayos tablet (Petition at 8). You indicate that that a generic version of Rayos might exhibit significant differences in PK profiles from the Rayos tablet, which may have an impact on pharmacodynamics and the therapeutic effect (Petition at 9).

We do not agree with your assertion that an ANDA with a different release mechanism than Rayos would necessarily result in significantly different pharmacodynamic and, consequently, therapeutic effects. This is because we do not believe that the particular release mechanism adopted by the reference listed drug, Rayos, is the only possible approach to achieve the same therapeutic effect. The overall therapeutic effect of a drug is dependent on its PK profile, and not necessarily its release mechanism. If the PK profiles of two pharmaceutically equivalent products are similar, a similar overall therapeutic effect can be assumed. If, as you state, a generic product using a different delayed-release mechanism exhibits significantly different PK properties, the current bioequivalence approach described in the background section above and in the Prednisone Bioequivalence Guidance should be able to capture the differences. Also, if a generic product is affected by the changes in pH in the intestinal tract, its PK profile is likely to be affected and the bioequivalence approach should detect the effect. In addition, a dissolution profile comparison will help to reveal the difference between the test and the reference formulations. In the event that a different delayed-release mechanism used by an ANDA applicant does result in in changes to the drug's overall PD profile and therapeutic effect, it should be captured by our current methodologies in assessing bioequivalence.

C. Bioequivalence Requirements — T_{max} and Food Effect

Because the Rayos product has a delayed-release mechanism, you request that, in addition to demonstrating bioequivalence criteria for C_{max} and AUC, FDA also require ANDA applicants to demonstrate comparable lag time and T_{max} between Rayos tablets and the proposed generic product (Petition at 9). You maintain that PK data should 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 (Petition at 9-10).

We do not agree that FDA should require any special or unusual bioequivalence requirements for ANDA applicants for generic products referencing Rayos. As discussed in the background section above, the criteria for bioequivalence are 90 percent confidence intervals of the ratios for AUC and C_{max} between the test and reference products falling within 80-125 percent. While we agree that T_{max} and T_{lag} (absorption lag time) define important points of the PK profile (i.e., the time to peak concentration of the drug and the start of drug absorption, respectively) for generic products referencing Rayos, FDA's policy is to not apply strict statistical criteria to evaluating T_{max} in bioequivalence studies due to the nature of the parameter. Unlike C_{max} and AUC, which are continuous variables, T_{max} is treated as a discrete measure of the rates of drug absorption from the test and reference products. As a result, T_{max} values are not amenable to the same statistical evaluation used for AUC and C_{max}. For these reasons, FDA decided not to impose statistical acceptance criteria on the parameter T_{max}. Thus, to the extent that your petition is requesting that FDA apply strict statistical criteria in its evaluation of T_{max}, FDA denies that request.

FDA routinely examines T_{max} and the entire PK profile (in addition to performing formal statistical equivalence tests on prespecified PK parameters, such as AUC and C_{max}) during the review process to determine whether any observed difference between test and reference products may result in a lack of therapeutic equivalence. To evaluate the difference in T_{max} or the PK profile between the test and reference products, FDA employs a variety of methods appropriate to the drug product for analysis. Furthermore, for ANDAs under review, FDA evaluates whether any difference might have clinical significance. The evaluation generally includes factors such as the indication, the dosing regimen, and whether the desired therapeutic effect is a function of steady state systemic drug concentrations or related to the time needed to achieve a threshold systemic concentration.

In addition to the examination of T_{max} and T_{lag}, a qualitative visual inspection of the entire concentration profile over time curve is routinely performed as part of the bioequivalence review of an ANDA. Any significant differences between plasma profiles are further investigated by review staff to determine if the differences may produce differences in therapeutic efficacy. We believe that our routine bioequivalence requirements for ANDA applicants along with our examination of T_{max} and T_{lag} should ensure that ANDAs are bioequivalent to the reference product, Rayos.

Similarly, we are denying your request that ANDA applicants for generic versions of Rayos be required to demonstrate an equivalent bioavailability profile to Rayos after T=4. Although the 4-hour delayed-release mechanism makes Rayos different than the immediate-release prednisone products, this characteristic does not provide any unique efficacy advantages or unacceptable safety concerns. Furthermore, FDA routinely evaluates the results of bioequivalence studies for potential impact of therapeutic equivalence that may be attributed to difference in the lag time or T_{max}. That process along with our standard bioequivalence requirements and assessments should ensure that ANDAs will have a similar PK profile to the RLD.

You claim that, unlike an immediate-release prednisone product, the Rayos product has a pronounced and substantial food effect that is a direct result of the special delayed-release mechanism of Rayos (Petition at 6-7). If Rayos is taken in the fed state, the tablets spend more time in the stomach than in the fasted state and Rayos is more effective if taken with food given the 4-hour lag time for the release of the drug product. You request that FDA require ANDA applicants to demonstrate bioequivalence under fed conditions because fed testing is critical to ensuring that the generic product is bioequivalent to Rayos (Petition at 10).

As stated in the Prednisone Bioequivalence Guidance, in addition to a fasted bioequivalence study, FDA also recommends a fed bioequivalence study for this product. The recommendation for both fasted and fed bioequivalence studies for this product is consistent with the draft guidance for industry *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA.*[15] The difference in the lag time or T_{max}, if observed in the fed bioequivalence study, will also be evaluated for its potential impact on the therapeutic equivalence. As a result, we grant your request that ANDA applicants referencing Rayos conduct bioequivalence studies in a fed state.

III. Conclusion

We have reviewed your petition and other relevant information available to the Agency. For the reasons stated above, your petition is granted in part and denied in part.

We are granting your request that FDA recommend ANDA applicants conduct bioequivalence studies under fed (in addition to fasting) conditions. We gave this clear recommendation in the Prednisone Bioequivalence Guidance. We are denying your request that FDA require ANDA applicants to submit data and information demonstrating that the proposed generic product has an equivalent lag time and T_{max}. We are also denying your request to require that ANDAs have an equivalent bioavailability profile to Rayos after t=4 hours. Under our current policy, we do not apply strict statistical criteria to evaluating T_{max} in bioequivalence studies due to the nature of the parameter. We do, however, routinely examine T_{max} and the entire PK profile during the review process to determine whether any observed difference between test and reference products may result in a lack of therapeutic equivalence.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[15] See note 9.