DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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OCT 3 2013

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Re: Docket No. FDA-2013-P-0574

Dear Dr. Barber:

This letter responds to your citizen petition received on May 10, 2013 (Petition). In the petition, you request that the Food and Drug Administration (FDA or the Agency) deny any abbreviated new drug application (ANDA) it receives for a generic version of Rapaflo (silodosin) Capsules, and in particular ANDA 204726 submitted by Sandoz Inc., unless the applicant demonstrates bioequivalence with respect to both silodosin and the metabolite KMD-3213G using the standard bioequivalence criteria. You also request that the Agency revise its draft guidance on bioequivalence testing for silodosin capsules to require that bioequivalence be demonstrated with respect to both silodosin and KMD-3213G.

We have carefully considered the information submitted in your petition and other relevant data.[1] For the reasons stated below, your petition is denied.

I. BACKGROUND

A. Rapaflo

Watson Laboratories, Inc., is the sponsor of the new drug application (NDA) for Rapaflo (silodosin) Capsules (NDA 022206), a prescription drug product indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).[2] The Agency approved Watson's NDA for Rapaflo Capsules, 4 milligrams (mg) and 8 mg, on October 8, 2008.[3] As set forth in the approved labeling for Rapaflo, a once-daily dose of the 8 mg strength, taken with a

[1] We also reviewed the comment you submitted to Docket No. FDA-2007-D-0369 concerning the Agency's draft bioequivalence guidance on silodosin capsules. We note that your comment raises the same issues and cites the same evidence as your petition.

[2] BPH is a noncancerous enlargement of the prostate that makes urination difficult and uncomfortable.

[3] Information regarding the basis for FDA's approval of Rapaflo (silodosin) Capsules is available on FDA's website at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022206s000TOC.cfm (last accessed Sept. 24, 2013).

meal, is recommended for patients without renal impairment or with mild renal impairment.[4] For patients with moderate renal impairment, a once-daily dose of the 4 mg strength (with a meal) is recommended.[5] Rapaflo is contraindicated in patients with severe renal impairment.[6]

The active ingredient in Rapaflo is silodosin, an alpha-1 adrenergic receptor antagonist. Silodosin undergoes extensive metabolism through glucuronidation, alcohol and aldehyde dehydrogenase, and cytochrome P450 3A4 (CYP3A4) pathways. Its main metabolite is a glucuronide conjugate, KMD-3213G, which has been shown in vitro to be active. KMD-3213G has an extended half-life (approximately 24 hours) and reaches plasma exposure approximately four times greater than that of silodosin.

B. Applicable Statutory and Regulatory Framework

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. § 355(j)), which established the ANDA approval process for generic drugs.[7] To obtain approval, an ANDA applicant is not required to provide independent evidence of the safety and effectiveness of the proposed generic drug product. Instead, the applicant relies on FDA's previous finding that the reference listed drug (RLD) is safe and effective.[8] The ANDA applicant must identify the listed drug on which it seeks to rely and, with limited exceptions, a drug product described in an ANDA must contain the same active ingredient, conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the listed drug it references.[9]

The ANDA applicant must also demonstrate that its proposed generic drug is bioequivalent to the listed drug it references.[10] Section 505(j)(8)(B)(i) of the FD&C Act states that a generic drug is bioequivalent to the listed drug if:

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[4] Approved Labeling for Rapaflo at 2, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022206s012lbl.pdf (last accessed Sept. 24, 2013).

[5] Id. at 2.

[6] Id. at 2-3.

[7] For purposes of this response, a generic drug is a new drug product for which approval is sought in an ANDA submitted under section 505(j) of the FD&C Act.

[8] A reference listed drug, or RLD, is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3). RLDs are identified in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, generally known as the Orange Book.

[9] Section 505(j)(2)(A) and (j)(4) of the FD&C Act. See also 21 CFR 314.94(a).

[10] See, e.g., section 505(j)(2)(A)(iv) of the FD&C Act (requiring "information to show that the new drug is bioequivalent to the listed drug"); 21 CFR 314.3 (defining *reference listed drug*); 21 CFR 314.94(a)(7) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the reference listed drug); 21 CFR 314.127(a)(6)(i) (providing that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the ANDA).

> the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses. . . .[11]

A showing that the active ingredient or therapeutic ingredient in the proposed generic drug reaches the site of drug action at a rate and to an extent not significantly different from that of the listed drug, along with other information required for approval, permits FDA to conclude that the proposed generic drug can be expected to perform the same way in the body as the listed drug. Bioequivalence testing determines whether differences in formulation (e.g., differences in inactive ingredients) between a proposed generic drug and the RLD have an impact on the rate and extent to which the active ingredient becomes available at the site of action.

The determination of bioequivalence for drug products whose primary mechanism of action depends on systemic absorption generally rests on a comparison of parent drug concentrations and, when appropriate, metabolite concentrations, in an accessible biologic fluid after administration of a single dose or multiple doses of each drug product to healthy volunteers. When this methodology is not appropriate, FDA may rely on other in vivo and/or in vitro methods to assess bioequivalence. Our regulations describe the methods in descending general order of accuracy, sensitivity, and reproducibility as follows: (1) in vivo pharmacokinetic studies of the active ingredient or active moiety and, when appropriate, its active metabolite(s), (2) in vivo pharmacodynamic effect studies of the active moiety and, when appropriate, its active metabolite(s), (3) comparative clinical endpoint studies, and (4) in vitro studies.[12] In addition, consistent with section 505(j)(8)(C) of the FD&C Act, section 320.24(b)(6) of our regulations states that FDA has the flexibility to use "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence" (21 CFR 320.24(b)(6)).

FDA has discretion to determine how the bioequivalence requirement should be met for a given product or class of products so long as its determination is not contrary to the governing statute and regulations and is based on a "reasonable and scientifically supported criterion" (*Schering Corp. v. Sullivan*, 782 F. Supp. 645, 651 (D.D.C. 1992)).[13] Courts have consistently upheld FDA's implementation of the FD&C Act's bioequivalence requirements (see, e.g., *Schering Corp. v. FDA*, 51 F. 3d 390, 397-400 (3rd Cir. 1995)).

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[11] See also 21 CFR 320.1(e) and 320.23(b).

[12] 21 CFR 320.24. Although a pharmacokinetic study measures the rate and the extent to which the drug is delivered to biological fluids (generally the bloodstream), a pharmacodynamic study measures effects associated with the delivery of the active ingredient to the site of action.

[13] See also *Fisons Corp. v. Shalala*, 860 F. Supp. 859, 866-67 (D.D.C. 1994) ("[T]he factual determination of how bioequivalence is determined properly rests within the FDA's discretion.").

C. Draft Silodosin Bioequivalence Guidance

FDA issued draft guidance on bioequivalence testing for silodosin capsules (Draft Silodosin BE Guidance) on April 8, 2013.[14] The Draft Silodosin BE Guidance recommends that ANDA applicants conduct two single-dose, two-way crossover in vivo studies with the 4 mg strength in normal, healthy males—one under fasting condition and the other under fed condition.[15] It further recommends that applicants measure both silodosin and its active metabolite, KMD-3213G, in each study. The Draft Silodosin BE Guidance advises applicants that they should demonstrate bioequivalence to silodosin based on the 90% confidence interval for the standard pharmacokinetic measures of area under the plasma concentration-time curve (AUC) and peak drug concentration (C_{max}).[16] Applicants are also advised to submit the AUC and C_{max} data for KMD-3213G as supportive evidence of comparable therapeutic outcome.

As with all Agency guidances, the Draft Silodosin BE Guidance, when finalized, will describe FDA's current thinking and should be viewed only as recommendations.[17] The Agency is not bound by the recommendations in the Draft Silodosin BE Guidance, however. It has the discretion to approve a generic product supported by bioequivalence data that otherwise meet the statutory and regulatory requirements described above.

II. DISCUSSION

Your petition requests that FDA deny any ANDA for a generic version of Rapaflo Capsules, and in particular ANDA 204726 submitted by Sandoz Inc., unless the applicant demonstrates bioequivalence to silodosin and its active metabolite, KMD-3213G, using strict statistical evaluation of the AUC and C_{max} measurements. The petition also asks that FDA revise the Draft Silodosin BE Guidance to state that ANDA applicants must demonstrate bioequivalence to both silodosin and KMD-3213G. We address below your arguments in support of these requests.

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[14] See 78 FR 20925 (Apr. 8, 2013). The Draft Silodosin BE Guidance is available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347041.pdf (last accessed Sept. 24, 2013).

[15] Because of safety concerns, the Draft Silodosin BE Guidance does not recommend in vivo bioequivalence testing with the 8 mg strength. An ANDA applicant can obtain a testing waiver for the 8 mg strength if it provides (1) acceptable bioequivalence studies on the 4 mg strength, (2) evidence demonstrating proportional similarity of the formulations across all strengths, and (3) acceptable in vitro dissolution testing of all strengths.

[16] FDA considers products bioequivalent when the 90% confidence intervals for the mean AUC and C_{max} measurements of the applicant's proposed generic product (e.g., silodosin) are entirely within 80% to 125% of the mean AUC and C_{max} measurements of the RLD (e.g., Rapaflo). See FDA guidance for industry on *Statistical Approaches to Establishing Bioequivalence* (Jan. 2001), available at http://www.fda.gov/downloads/Drugs/Guidances/ucm070244.pdf (last accessed Sept. 24, 2013).

[17] 21 CFR 10.115(d)(3) ("Although [final] guidance documents do not legally bind FDA, they represent the Agency's current thinking. Therefore, FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence.").

A. FDA Guidance on Bioequivalence Studies for Drugs with Active Metabolites

You state that FDA should require ANDA applicants to demonstrate bioequivalence with respect to KMD-3213G because it contributes meaningfully to the overall therapeutic benefit, safety, and effectiveness of silodosin (Petition at 1, 6-7). In support of this statement, you cite a section in our March 2003 guidance, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations* (BA/BE Guidance),[18] that describes the Agency's approach to bioequivalence testing for drugs with active metabolites. You interpret this section as recommending that ANDA applicants demonstrate bioequivalence to any metabolite that contributes meaningfully to a drug's pharmacodynamics. We disagree with your interpretation.

As explained in the BA/BE Guidance, we generally recommend that ANDA applicants measure only the parent drug released from the dosage form (e.g., silodosin) in a bioequivalence study. There are two exceptions to this general recommendation, however, that address situations in which it is appropriate to measure a drug's metabolites. The first exception is when the parent drug levels are too low to allow reliable analytical measurement in blood, plasma, or serum for an adequate length of time.[19] For drugs falling within this exception, the BA/BE Guidance recommends that ANDA applicants measure the parent drug's metabolites and subject the metabolite data to a confidence interval analysis for bioequivalence demonstration.[20] The second exception is when a metabolite is formed as a result of gut wall or other presystemic metabolism and contributes meaningfully to safety and/or efficacy.[21] With respect to this exception, the BA/BE Guidance explains:

> If the metabolite contributes meaningfully to safety and/or efficacy, we also recommend that the metabolite and the parent drug be measured. When the relative activity of the metabolite is low and does not contribute meaningfully to safety and/or efficacy, it does not have to be measured. We recommend that the parent drug measured in these BE studies be analyzed using a confidence interval approach. *The metabolite data can be used to provide supportive evidence of comparable therapeutic outcome.*[22]

You assert that silodosin "fits neatly within" the second exception (Petition at 6). We agree. The available scientific evidence on the bioavailability of silodosin indicates that KMD-3213G is formed, at least to some extent, as a result of presystemic metabolism. The evidence also suggests that the metabolite makes a meaningful contribution to silodosin's overall activity. Thus, silodosin satisfies all the elements of the second exception.

The Agency disagrees, however, that ANDA applicants should be required to demonstrate bioequivalence to KMD-3213G using strict statistical evaluation of the AUC and C_{max} measurements merely because silodosin falls within the second exception. You misread the

[18] Available at http://www.fda.gov/downloads/Drugs/Guidances/ucm070124.pdf (last accessed Sept. 24, 2013).

[19] BA/BE Guidance at 18.

[20] Id.

[21] Id.

[22] Id. (emphasis added).

exception as supporting this outcome. The second exception recommends that ANDA applicants *measure* metabolites that contribute meaningfully to safety or efficacy. But unlike the first exception, it does not ask ANDA applicants to *analyze* the metabolite data for *bioequivalence*.

Properly understood, the second exception recommends that ANDA applicants analyze *only* the parent drug (e.g., silodosin) as a means to demonstrate bioequivalence. The rationale for this recommendation is two-fold. First, the parent drug can be reliably measured in blood, plasma, or serum (otherwise, the first exception would apply). Second, the concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, and therefore is a better indicator for purposes of determining bioequivalence. Based on the available scientific evidence, we have determined that this rationale applies to silodosin.

Accordingly, we decline to require that ANDA applicants for generic silodosin capsule products demonstrate bioequivalence with respect to KMD-3213G simply because the metabolite contributes meaningfully to silodosin's overall pharmacologic activity. Such a requirement is not justified by the second exception to our general approach to bioequivalence testing for orally administered drugs. ANDA applicants should measure KMD-3213G and provide the metabolite data to FDA as supportive evidence of bioequivalence, however. This approach is consistent with the plain language of the BA/BE Guidance, and is the approach we have proposed, and will continue to follow, in the Draft Silodosin BE Guidance.

B. The Contribution of KMD-3213G to Silodosin's Therapeutic Effect During the Latter Half of the Dosing Period

You assert that FDA should require ANDA applicants to demonstrate bioequivalence with respect to KMD-3213G "because [the metabolite] functions as an active ingredient once in systemic circulation during the latter half of the concentration-time profile" (Petition at 6). In particular, you assert that the half-life data and exposure profile data suggest that KMD-3213G is responsible for "virtually all" of silodosin's therapeutic effect during the latter half of the dosing period (Petition at 7).

We find that there is insufficient evidence to support this assertion. To determine how much KMD-3213G contributes to silodosin's therapeutic effect during the latter half of the dosing period, we would need data on the effect that exposure to silodosin and KMD-3213G during this period has on the International Prostate Symptom Score (IPSS) of BPH patients.[23] Although the petition provides some exposure-related information for hours 12 to 24 of the dosing period, it does not provide any IPSS data for this period. Nor are we aware of any other studies that provide such data. Consequently, the Agency does not have sufficient evidence before it to conclude that KMD-3213G is responsible for most of silodosin's activity in the second half of the dosing period.

However, even if the evidence showed that the metabolite was in fact responsible for virtually all of silodosin's therapeutic effect during the latter half of the dosing period, we still would not require that ANDA applicants demonstrate bioequivalence to KMD-3213G. Given that most of

[23] The change from baseline to last observation carried forward in the IPSS was the primary endpoint in the phase 3 studies that were conducted to demonstrate the clinical efficacy of silodosin in treating BPH.

the absorption and pharmacologic activity of silodosin and KMD-3213G occurs in the first half of the dosing period, we believe it is unlikely that the pharmacologic activity of KMD-3213G during the latter half of the dosing period has a significant impact on the safety or efficacy of silodosin. Furthermore, we generally base bioequivalence determinations on the parent drug whenever it can be reliably and accurately measured. As noted above, the rationale for this approach is that the parent drug is more sensitive to changes in formulation performance than a metabolite. Because silodosin is readily measured in plasma, the Draft Silodosin BE Guidance recommends that it be used for purposes of demonstrating bioequivalence. We are not persuaded by your petition to change this recommendation.

C. Safety Implications of Over- or Under-Dosing with KMD-3213G

You state that we should require ANDA applicants to demonstrate bioequivalence to KMD-3213G to ensure that patients are not over- or under-dosed with the metabolite (Petition at 7). You contend that the proper dosing of KMD-3213G is an important safety issue, particularly for BPH patients with moderate renal impairment (Petition at 7).[24] You further contend that a failure to demonstrate bioequivalence to both silodosin and KMD-3213G could result in "serious consequences to patient health" (Petition at 7).

Again, we find that there is insufficient evidence to support this contention. In particular, there is no information in the petition that explains how different plasma concentrations of KMD-3213G affect patient health. Nor are we aware of any studies that establish the exposure-response relationship for silodosin or KMD-3213G. Absent a clear, evidence-based understanding of the exposure-response relationship for these compounds, we have no basis to conclude that over- or under-dosing with KMD-3213G poses a safety risk.

In addition, we believe that your petition overstates the likelihood that significant over- or under-dosing of KMD-3213G will occur unless we require that ANDA applicants demonstrate bioequivalence to the metabolite. As discussed above, the Draft Silodosin BE Guidance advises applicants to demonstrate bioequivalence to silodosin and to submit the AUC and C_{max} data for KMD-3213G as supportive evidence. Consistent with long-standing Agency practice, we will analyze the data for both compounds using the same statistical approach. In the event that the silodosin data satisfy the 90% confidence interval requirement but the KMD-3213G data do not, we will conduct additional analyses of the metabolite data to determine whether they support a finding of bioequivalence. Such extensive analysis of the metabolite data minimizes the possibility that FDA could approve a non-equivalent version of Rapaflo in which patients are significantly over- or -under-dosed with KMD-3213G.

III. CONCLUSION

For the reasons discussed in this response, your petition is denied. We are not persuaded by the petition that ANDA applicants for generic silodosin capsules need to demonstrate bioequivalence with respect to the active metabolite KMD-3213G. We therefore will not revise the Draft Silodosin BE Guidance to include such a recommendation. Instead, we will continue to

[24] As indicated in section I.A of this response, a once-daily dose of 4 mg silodosin, taken with a meal, is recommended for patients with moderate renal impairment.

recommend that ANDA applicants measure KMD-3213G in their bioequivalence studies, and that they include the metabolite data in their ANDAs as supportive evidence. Regarding your request that we refuse to approve any ANDA for a generic version of Rapaflo unless the applicant demonstrates bioequivalence with respect to both silodosin and KMD-3213G, it is further denied.

Sincerely,

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