DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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Re: Docket No. FDA-2013-P-0198

Dear Mr. Kukulka and Mr. Muldoon:

This letter responds to your citizen petition dated February 15, 2013 (the Petition), requesting that the Food and Drug Administration (FDA or the Agency) refrain from approving any abbreviated new drug application (ANDA) that relies upon Dexilant (dexlansoprazole) delayed-release capsules as the reference listed drug (RLD) unless it includes data showing bioequivalence using the partial area under the plasma concentration-time curve (pAUC) metrics of $pAUC_{0\text{-}2h}$ and $pAUC_{2\text{-}10h}$ in addition to conventional metrics.[1] We have carefully considered the issues raised in your Petition and the supplement to your Petition dated April 12, 2013. For the reasons stated below, your Petition is denied.

I. BACKGROUND

A. Dexilant (dexlansoprazole) Delayed-Release Capsules and Proton Pump Inhibition

Takeda Pharmaceuticals U.S.A., Inc., (Takeda) holds new drug application (NDA) 22-287, for Dexilant (dexlansoprazole) Delayed-Release Capsules, 30 mg and 60 mg. Dexilant is a proton pump inhibitor (PPI) that suppresses gastric acid secretion by specific inhibition of the (H^+, K^+)-ATPase in the gastric parietal cell. By acting specifically on the proton pump, dexlansoprazole blocks the final step of acid

[1] Petition at 3.

production.[2] Once-daily dosing of Dexilant is indicated for healing of all grades of erosive esophagitis (EE); maintaining healing of EE and relief of heartburn; and treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease. Dexilant can be taken without regard to food and should be swallowed whole or, alternatively, sprinkled on applesauce.[3]

Dexilant is a dual delayed-release formulation with two types of enteric-coated granules with different pH-dependent dissolution profiles. Twenty-five percent of the dose is released in the upper intestinal tract when the local pH reaches approximately 5.5. The remaining 75 percent of the dose is released in the lower intestinal tract when the local pH reaches approximately 6.75. According to Dexilant's product labeling, Dexilant's pharmacokinetic (PK) profile has two distinct peaks that correspond to the dual release of the drug in the upper and lower intestinal tracts: the first peak occurs 1 to 2 hours after administration, and the second peak occurs 4 to 5 hours after administration.[4] Pre-approval studies of Dexilant showed variability in the PK profile. For example, under fed conditions, drug release was delayed, and there was little systemic exposure in the first three hours post-dose compared to fasting conditions.[5]

B. Applicable Statutory and Regulatory Framework

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created 505(j) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(j)). The Hatch-Waxman Amendments reflect Congress' efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962" with new incentives for drug development in the form of marketing exclusivity and patent term extensions.[6] Section 505(j) of the FD&C Act established an abbreviated approval pathway for a drug product that is the same as a previously approved drug (the RLD) with respect to active ingredient, dosage form, route of administration, strength, labeling, and conditions of use, among other characteristics. An ANDA applicant also must demonstrate that its proposed product is bioequivalent to the

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[2] Dexilant Package Insert at 5.

[3] Dexilant Package Insert at 1-2.

[4] Dexilant Package Insert at 6.

[5] FDA Clinical Pharmacology and Biopharmaceutics Review of dexlansoprazole delayed-release capsules (NDA 22-287) (Clinical Pharmacology Review) at 74-80 and 142-54, July 21, 2008 (available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022287s000_ClinPharmR_P1.pdf and http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022287s000_ClinPharmR_P2.pdf).

[6] *See* House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

RLD.[7] An applicant that can meet the requirements under section 505(j) for approval may reference the Agency's finding of safety and effectiveness for the RLD, and need not repeat the extensive nonclinical and clinical investigations required for approval of a stand-alone NDA submitted under section 505(b)(1) of the FD&C Act.

The statute, regulations, and case law give FDA significant flexibility in determining how an ANDA applicant can show that its proposed generic drug is bioequivalent to the RLD it references. Section 505(j)(8)(B)(i) of the FD&C Act states that a generic drug is bioequivalent to the listed drug if:

> 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 . . . .[8]

Congress also recognized that some drugs do not reach their site of action through absorption into the bloodstream. Thus, section 505(j)(8)(C) of the FD&C Act states the following:

> For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.

In 21 CFR 320.1(e), FDA defines bioequivalence (in pertinent part) as:

> ...the absence of a significant difference in the rate and extent to which the active ingredient or active moiety . . . becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

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 can determine whether differences in formulation (e.g., differences in inactive ingredients) between a proposed

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[7] 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"); see also 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).

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

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 of drug products whose primary mechanism of action depends on systemic absorption (e.g., two solid oral dosage forms) generally rests on a comparison of drug and/or metabolite concentrations in an accessible biologic fluid, such as blood or urine, after administration of a single dose or multiple doses of each drug product to healthy volunteers. When this methodology is not appropriate, FDA may, as described in provisions of the FD&C Act and 21 CFR part 320, rely on other in vivo and/or in vitro methods to assess bioequivalence. FDA regulations describe these methods in descending order of accuracy, sensitivity, and reproducibility. They include (1) in vivo PK studies, (2) in vivo pharmacodynamic (PD) effect studies, (3) clinical endpoint studies, and (4) in vitro studies.[9] In addition, consistent with section 505(j)(8)(C) of the FD&C Act, section 320.24(b)(6) of the regulations states that FDA has the flexibility to use "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence."

It is well-accepted that FDA has considerable discretion in determining how the bioequivalence requirement is met. FDA's discretion need only be based on a "reasonable and scientifically supported criterion, whether [the Agency] chooses to do so on a case-by-case basis or through more general inferences about a category of drugs. . . " (*Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 218 (D.D.C. 1996) (quoting *Schering v. Sullivan Corp.*, 782 F. Supp. 645, 651 (D.D.C. 1992), vacated as moot sub nom, *Schering Corp. v. Shalala*, 995 F.2d 1103 (D.C. Cir. 1993))). Courts have expressly upheld FDA's implementation of the FD&C Act's bioequivalence requirements (see, e.g., *Schering Corp. v. FDA*, 51 F.3d 390 at 397-400 (3d Cir. 1995); *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994)).

C. Draft Guidance on Dexlansoprazole

FDA's *Draft Guidance on Dexlansoprazole* provides recommendations on how to design bioequivalence studies to support ANDAs for dexlansoprazole delayed-release capsules (Dexlansoprazole Draft Guidance).[10] The Dexlansoprazole Draft Guidance recommends three studies using the 60 mg capsule: one fasting study and one fed study with the intact capsule, and one fasting study with the capsule sprinkled onto applesauce. Each study should be a single-dose, two-way crossover in vivo study measuring dexlansoprazole in

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[9] 21 CFR 320.24. A PK study measures the rate and the extent to which the drug is delivered to biological fluids (generally the bloodstream); a PD study measures effects associated with the delivery of the active ingredient to the site of action.

[10] This draft guidance published on FDA's website in June 2011. When finalized, it will represent FDA's current thinking on this topic (available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm).

the plasma of healthy males and nonpregnant females. Bioequivalence should be demonstrated based on a 90 percent confidence interval.[11] In vivo studies using the 30 mg strength may be waived if certain criteria are met, including acceptable bioequivalence studies on the 60 mg strength, acceptable in vitro dissolution testing of all strengths, and proportional similarity of the formulations across both strengths.[12]

II. DISCUSSION

You request that FDA refrain from approving any ANDA for dexlansoprazole delayed-release capsules referencing Dexilant unless the ANDA includes data demonstrating bioequivalence using partial AUC metrics, in addition to the conventional metrics. Specifically, you request that bioequivalence be demonstrated using $pAUC_{0\text{-}2h}$ and $pAUC_{2\text{-}10h}$ in addition to $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and peak plasma concentration (C_{max}). We address the arguments you have made in support of your request below.

A. Dexilant's Multiphasic, Modified-Release Properties Are Not "Clinically Significant"

You describe Dexilant as a multiphasic, modified-release drug product, citing the product labeling.[13] You further state that this information is included in the labeling because it communicates "important chemical or physical information" and represents what the Agency has determined to be the "clinically significant pharmacokinetics" of the drug product.[14] You explain that Dexilant was designed to prolong the plasma-concentration profile of dexlansoprazole to "counter sequential activations and later regeneration of proton pumps" and provide an extended duration of acid suppression.[15] Specifically, Dexilant promotes absorption of the first type of delayed-release granule in the proximal small intestine and absorption of the second type of delayed-release granule at a specific distal location within the small intestine before entrance into the colon. You contend that

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[11] FDA considers products bioequivalent when the 90 percent confidence intervals for the test/reference PK parameter ratios are entirely within an 80 to 125 percent acceptance interval. *See* FDA guidance for industry *Statistical Approaches to Establishing Bioequivalence*, available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[12] Dexlansoprazole Draft Guidance at 1-2.

[13] The labeling states in relevant part, "DEXILANT is … a dual delayed-release formulation in capsules for oral administration. The capsules contain dexlansoprazole in a mixture of two types of enteric-coated granules…The dual delayed-release formulation of DEXILANT results in a dexlansoprazole plasma concentration-time profile with two distinct peaks; the first peak occurs 1 to 2 hours after administration, followed by a second peak within 4 to 5 hours." Dexilant Package Insert at 5-6.

[14] Petition at 9.

[15] Petition at 6.

a generic product that does not provide a second phase of release in the distal region of the small intestine is not therapeutically equivalent[16] to Dexilant.[17]

FDA does not agree that Dexilant's multiphasic, modified-release properties result in "clinically significant pharmacokinetics" which must be replicated in generic versions of Dexilant. Dexlansoprazole has a half-life of 1 to 2 hours, and there is no drug accumulation after multiple dosing. As noted in the product labeling, the first peak occurs at around 1 to 2 hours and the second peak at around 4-5 hours.[18] By 12 to 16 hours, only low concentrations of dexlansoprazole are found in plasma. However, proton pump activity (i.e., acid release) is suppressed for at least 24 hours after a single dose of Dexilant, as evidenced by the prolonged PD effect of intragastric pH, a measurement of the amount of gastric acid in the stomach.[19] Because the PD effect is more prolonged than the time that dexlansoprazole is present in plasma, a dual peak in the PK profile is not expected to have an impact on the PD profile or clinical outcome.[20] Thus, minor changes in the PK profile would not be expected to result in clinically meaningful changes in the pharmacodynamic effects of a generic version of Dexilant.

In addition, food-effect studies of dexlansoprazole demonstrate that administering the drug at different times in relation to food results in substantial changes in the PK profiles. Specifically, the time to reach peak plasma concentration (T_{max}) is delayed by 2 to 4 hours when the drug is administered after a meal compared to when it is administered in a fasted state. However, these changes in PK profiles in the presence of food do not result in a clinically meaningful difference in PD (intragastric pH) parameters.[21] Based on

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[16] Drugs are considered to be therapeutically equivalent "only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling" based on, among other things, a showing that the two products are bioequivalent. *Approved Drug Products with Therapeutic Equivalence Evaluations* (2013) at vii.

[17] Petition at 12-15.

[18] Dexilant Package Insert at 6.

[19] Clinical Pharmacology Review at 56-62.

[20] In a study comparing Dexilant to lansoprazole, which does not have multiphasic, modified-release properties, there was no clear advantage in healing of erosive esophagitis between the two products. Dexilant Package Insert at 8 (Clinical Studies Section 14.1, Table 5).

[21] The percentage of time intragastric pH was greater than 4 over the 24-hour dosing interval was 57 percent when administered after food compared to 64 percent in the fasting group. Similarly, when administered 5 or 30 minutes before a meal, the percentages of time intragastric pH was greater than 4 over the 24-hour dosing interval were 62 percent and 66 percent, respectively. The difference in PD parameters was driven largely by the periods 0 to 4 and 4 to 9 hours post-dose. The four feeding regimens have less variation 9 or more hours after dosing. *See* Clinical Pharmacology Review at 56-62.

these data, the Dosing and Administration section of the Dexilant labeling states that no significant differences in mean intragastric pH were observed between fasted and various fed conditions and that Dexilant can be taken without regard to food.[22] Because the product is similarly effective in the fasting and fed states despite differences in PK profiles, FDA disagrees that Dexilant's dual peaks are an important feature that must be replicated for generic versions to be bioequivalent to Dexilant.

We note that although the dual-releasing feature does not need to be replicated, the general plasma-concentration profile should not show significant differences between Dexilant and a generic product. This can be evaluated using the traditional PK parameters of AUC and C_{max}. A generic product with a single peak may be approved if it meets the bioequivalence criteria for AUC and C_{max}. AUC and C_{max} ensure that a generic product referencing Dexilant would not differ significantly from Dexilant in terms of the extent of drug absorption (i.e., maintenance of sustained drug concentrations in plasma) and rate of drug absorption, respectively.

Differences in lag time can be judged from a qualitative assessment of T_{max}, which is evaluated in every bioequivalence study to help determine whether any differences between test and reference products would be clinically meaningful. Differences in dissolution test results can also help differentiate between products with different drug release profiles. The dissolution test is conducted in an acid stage and a buffer stage to evaluate the strength of the enteric coat. In addition, dissolution must also be conducted at a range of pH values using multiple media. This will help to evaluate drug release at various pH values. In sum, FDA believes that the traditional PK parameters of AUC and C_{max} are sufficient to ensure bioequivalence between Dexilant and a generic version of Dexilant.

B. Partial AUC Metrics are Not Necessary to Ensure Same Onset of Activity

You state that the T_{max} for Dexilant does not occur until drug from the second type of granule has begun to be released. You maintain that because T_{max} does not reflect the first phase of release, a partial AUC metric is necessary to assess the absorption of the first, early-release component of the generic version of Dexilant to ensure it has the same onset of activity as Dexilant and is bioequivalent to Dexilant with regard to each phase of release of dexlansoprazole.[23]

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[22] Dexilant Package Insert at 7.

[23] Petition at 16-17.

We disagree that a partial AUC metric is necessary for a generic version of Dexilant to be bioequivalent to Dexilant because the dual-release formulation is not a "clinically significant" feature of Dexilant. Studies conducted by Takeda in support of approval showed variations in the dual-peak features of Dexilant's PK profile. For example, in the fasted state, two studies showed two distinct peaks, but another study did not. Similarly, in the fed state, one study showed two distinct peaks and one did not. Despite variability in the PK profile, corresponding changes in PD effect, as measured by intragastric pH, and in healing of erosive esophagitis were not observed.[24,25] As stated elsewhere in this response, FDA evaluates AUC and C_{max} along with a qualitative evaluation of T_{max} and an assessment of the dissolution profile to determine bioequivalence. For a generic drug that does not show significant differences from Dexilant in these attributes, the T_{max} and in vivo drug release profile are expected to be similar. Therefore, an additional partial AUC metric is not necessary to ensure bioequivalence for generics to Dexilant.

C. Partial AUC Metrics Recommended for Other Multiphasic, Modified-Release Drug Products Are Not Relevant to Dexlansoprazole

Citing the draft bioequivalence recommendations for Adderall XR, Metadate CD, and Concerta, you state that for products approved and labeled for multiphasic, modified-release, the Agency has consistently recognized the need for statistical analysis of partial AUC metrics to ensure that proposed generics replicate the basic design of the RLD. You maintain that partial AUC metrics are necessary to ensure bioequivalence for these drug products because they contain immediate-release and delayed-release components; are designed to achieve both rapid onset of activity and sustained activity throughout the day; and do not show unusual accumulation at steady-state.[26] You assert that Dexilant has the same type of dual-release mechanism, and thus traditional bioequivalence metrics are not adequate to ensure bioequivalence for proposed generic versions of Dexilant.

The examples of multiphasic, modified-release drugs cited in the Petition — Adderall XR, Metadate CD, and Concerta — are indicated for treatment of attention deficit hyperactivity disorder (ADHD), for which the timing of drug release is critically important for efficacy.[27,28] In other words, there is a clear correlation between drug

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[24] FDA Clinical Pharmacology Review at 74-80 and 142-54.

[25] Dexilant Package Insert at 8 (Clinical Studies Section 14.1, Table 5). In a study comparing Dexilant to lansoprazole, which does not have multiphasic, modified-release properties, there was no clear advantage in healing of erosive esophagitis between the two products.

[26] Petition at 10-11.

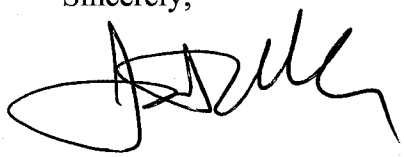
[27] We note that the Petition cites several other examples in which FDA has required partial AUC analysis, including Ritalin LA, Focalin XR, and Ambien CR. Similar to Adderall XR, Metadate CD, and Concerta,

concentration and PD effect, and any increase or decrease in the PK profile produces an immediate effect on the PD response.[29] As discussed earlier in this response, dexlansoprazole does not show such a correlation, and the examples cited in the Petition are not relevant to your request.

III. CONCLUSION

For the reasons explained above, your Petition is denied.

Sincerely,



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

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these are drug products in which the timing of drug release is important and there exists a clear correlation between drug concentration and PD effect.

[28] The Petition also cites Asacol HD as an example in which FDA has required the use of partial AUC metrics where the RLD displays time-dependent localization of absorption within the gastrointestinal tract. Petition at 8. Asacol HD is not relevant to an analysis of partial AUC metrics for Dexilant because Asacol HD is a locally-acting drug product and the partial AUC for Asacol HD is used to demonstrate local drug release in the colon; plasma levels are tertiary to any clinical activity of Asacol HD. *See* FDA's August 20, 2010, Citizen Petition Response on Asacol, Asacol HD, and Pentasa (Docket Nos. FDA-2010-P-0111 and FDA-2008-P-0507) and FDA's "Draft Guidance on Mesalamine," which published on FDA's website in September 2012. When finalized, it will represent FDA's current thinking on this topic (available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm).

[29] *See e.g.,* FDA's June 22, 2012, Citizen Petition Response on Adderall XR (Docket No. FDA-2005-P-0120), FDA's July 19, 2012, Citizen Petition Response on Metadate CD (Docket No. FDA-2004-P-0151), and FDA's July 19, 2012, Citizen Petition Response on Concerta (Docket No. FDA-2004-P-0290), available at http://www.regulations.gov.