Takeda

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VIA HAND DELIVERY
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

Takeda Pharmaceuticals U.S.A., Inc. ("Takeda") respectfully submits this Citizen Petition under 21 USC 355 and 21 CFR 10.30, among other provisions of law, to request that the Commissioner of Food and Drugs take the actions described below with respect to any abbreviated new drug application ("ANDA") that references DEXILANT (dexlansoprazole) delayed-release capsules for oral use ("DEXILANT").

Takeda is the sponsor of DEXILANT, as well as the related product, PREVACID (lansoprazole) delayed-release capsules ("PREVACID"). Both products contain as their active ingredient a proton pump inhibitor ("PPI"), and are approved to treat heartburn and heartburn-related conditions. While both are delayed-release dosage forms, DEXILANT differs from PREVACID in that it includes a modified release mechanism that provides two phases of drug release during the dosing interval.

In the past 12 months, the Food and Drug Administration ("FDA" or "the Agency") has issued several important decisions and guidance documents for multiphasic, modified-release drug products. Specifically, on September 14, 2012, the Agency announced the publication of product specific bioequivalence ("BE") recommendations for Adderall XR, Metadate CD, and Concerta.[1] The guidance documents incorporate the reasoning of the citizen petition responses regarding these products issued in June and July 2012.[2] A similar set of BE recommendations were

[1] *See* Draft and Revised Draft Guidances for Industry Describing Product-Specific Bioequivalence Recommendations; Availability, 77 FR 56851 (September 14, 2012).

[2] FDA Citizen Petition Response, Metadate CD and Concerta, Docket Nos. FDA-2004-P-0151 and FDA-2004-P-0290 (July 19, 2012) ("Metadate CD and Concerta Petition Response"); FDA Citizen Petition Response, Adderall XR, Docket No. FDA-2005-P-0120 (June 22, 2012) ("Adderall Petition Response").

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issued for Focalin XR in March 2012.[3] These documents reflect a carefully considered FDA determination that where a dosage form contains a dual-release mechanism, and is designed to achieve both rapid onset of activity and sustained activity throughout the day, additional pharmacokinetic ("PK") metrics are needed to ensure true bioequivalence to the reference listed drug ("RLD").

As shown in the approved labeling, DEXILANT is likewise formulated to provide two distinct phases of drug release:

> DEXILANT is supplied as a dual delayed-release formulation in capsules for oral administration. The capsules contain dexlansoprazole in a mixture of two types of enteric-coated granules with different pH-dependent dissolution profiles.[4]
> ***
> 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.[5]

To be considered bioequivalent, and to carry the same labeling as DEXILANT, a generic product approved under an ANDA must exhibit the same dual delayed-release features and exhibit the same bioavailability as the RLD with respect to both phases of release.

In June 2011, FDA published a guidance document in draft form providing product-specific BE recommendations for generic versions of DEXILANT (the "Draft Guidance").[6] The Draft Guidance for proposed generics to DEXILANT predates the recent decisions regarding dual-release dosage forms and has not been updated to reflect the Agency's recent decisions. In particular, the Draft Guidance for DEXILANT specifies no additional PK parameters beyond the conventional metrics. In its current form, the Draft Guidance suggests that the 90% confidence interval ("CI") must be met

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[3] *See* Draft Guidance on Dexmethylphenidate Hydrochloride (Mar. 2012) ("Draft Guidance on Focalin XR"), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM296744.pdf.

[4] *See* Tab 1, DEXILANT Package Insert at 11 Description, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022287s014lbl.pdf.

[5] *See id.* at 12.3 Pharmacokinetics.

[6] *See* "Draft Guidance on Dexlansoprazole" (Jun. 2011), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM261519.pdf.

only with respect to C_{max}, AUC_{0-t} and AUC_{0-inf}.[7] As detailed in FDA's recent decisions, these parameters are unable to adequately describe both phases of drug release for a product that is approved and labeled for bimodal drug release. This is particularly the case when, as here, C_{max} does not occur until the second phase of release.[8]

Approval of an ANDA referencing DEXILANT that does not include analysis of an additional PK metric may result in the marketing and use of a non-equivalent product. Takeda therefore requests that FDA refrain from approving any ANDA for dexlansoprazole dual delayed-release capsules unless it includes data demonstrating BE using additional partial AUC metrics[9] designed to measure both distinct phases of drug release.

ACTION REQUESTED

Takeda respectfully requests that FDA refrain from approving any ANDA referencing DEXILANT unless it includes data showing bioequivalence using partial AUC metrics in addition to AUC_{0-t}, AUC_{0-inf}, and C_{max}. These partial AUC metrics should include $pAUC_{0-2h}$ and $pAUC_{2-10h}$, in addition to the conventional metrics.

STATEMENT OF GROUNDS

I. BACKGROUND

A. The reference drug product

DEXILANT is a dual delayed-release, proton pump inhibitor ("PPI"),[10] exhibiting biphasic PK.[11] It is approved for use in adults for the healing of erosive esophagitis ("EE"). If untreated or undertreated, EE can lead to esophageal cancer and other serious

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[7] The Draft Guidance recommends three *in vivo* PK studies (fed, fasting and fasting-sprinkle-in-apple sauce), using single-dose, two-way crossover design, and identifies dexlansoprazole in plasma as the study analyte. The Draft Guidance states that bioequivalence is to be determined based on statistical significance at the 90% CI, but does not recommend any additional PK parameters.

[8] Takeda submitted comments to FDA recommending modifications to the Draft Guidance. *See* FDA-2007-D-0369-0098 (Dec. 14, 2012). As of the date of this Petition, FDA has not proposed any changes to the Draft Guidance based on Takeda's comments.

[9] Partial AUC refers to an area under the PK curve that is delimited by an (additional) relevant time parameter. In other words, it is a metric that describes a subcomponent (subset) of the AUC_{0-inf} data set.

[10] *See* Tab 1, DEXILANT Package Insert at 11 Description.

[11] *See id.* at 12.3 Pharmacokinetics.

conditions. DEXILANT is also indicated for maintenance of healing of EE, and for the treatment of symptomatic nonerosive gastroesophageal reflux disease ("GERD").[12] It can be administered as an intact capsule, or can be opened and the granules sprinkled on a tablespoon of applesauce.[13]

DEXILANT "is formulated in modified release."[14] The modified release formulation consists of two types of delayed-release granules contained within a single capsule. The enteric coating of the early-releasing granules provides protection to the drug while passing through the stomach into the intestinal tract, where release is rapid. The late-releasing granules are designed to release dexlansoprazole in the lower intestinal tract, contributing to a second, discrete phase of release. Because of this dual delayed-release feature, the initial drug release occurs within 1 to 2 hours of administration, followed by the second phase of release within 4 to 5 hours post-dose.[15] The early-releasing granules in the DEXILANT capsule provide 25% of the dexlansoprazole dose, and the late-releasing granules provide 75% of the dose.[16]

The active ingredient – dexlansoprazole – is the *R*-enantiomer of the racemic mixture, lansoprazole.[17] Lansoprazole and dexlansoprazole both specifically inhibit (H+, K+)-ATPase pumps in the gastric parietal cells that line the stomach, thereby suppressing gastric acid secretion.[18]

The racemic form of the drug, lansoprazole, is the active ingredient in PREVACID. Unlike DEXILANT, PREVACID contains a single delayed-release formulation of enteric coated granules, designed to provide rapid drug release after the granules leave the stomach and enter the upper intestinal tract. Lansoprazole is acid-

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[12] *See id.* at 1 Indications and Usage.

[13] *See id.* at 2 Dosage and Administration.

[14] *See* DEXILANT Approval Package, Clinical Pharmacology and Biopharmaceutics Review at 3, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022287s000_ClinPharmR_P1.pdf. The United States Pharmacopeia ("USP") describes two kinds of "modified dosage forms," namely "delayed release" and "extended release." "Delayed release" capsules contain enteric coated granules to protect the active pharmaceutical ingredient under acid conditions. In contrast, "extended release" capsules are formulated to make the contained active pharmaceutical ingredient available over an extended period of time. USP 35 <1151> 768. DEXILANT is labeled as "delayed release" with "dual delayed release" to indicate two different kinds of enteric coated granules with different release profiles, and conforms to USP specifications as a "modified release dosage form."

[15] *See* Tab 1, 12.3 Pharmacokinetics.

[16] *See* DEXILANT Approval Package, Clinical Pharmacology and Biopharmaceutics Review at 6.

[17] *See* Tab 1, at 11 Description.

[18] *See id.* at 12.1 Mechanism of Action.

labile and, as such, it requires an enteric-coated formulation to prevent degradation of the molecule in the acidic stomach environment. For PREVACID, once the granules release the drug, absorption of lansoprazole is rapid, with time to maximal plasma concentration achieved by 2 hours post-dose.

Elimination of lansoprazole is also rapid. The plasma half-life of lansoprazole is about 1.5 hours and plasma concentrations typically fall below the level of detection by 12 hours post-dose. Furthermore, the *S*-enantiomer (S-lansoprazole) is more rapidly cleared from the plasma than dexlansoprazole. Dexlansoprazole is therefore the predominant circulating enantiomer and is responsible for the majority of the *in vivo* pharmacological effects of PREVACID.[19]

Clinically it has been shown that S-lansoprazole exhibits a lower pharmacological response (suppression of gastric acid secretion) compared with an equivalent dose of dexlansoprazole. The diminished pharmacodynamic effect of S-lansoprazole appears to be based on its rapid clearance compared to dexlansoprazole *in vivo*.[20] Takeda therefore developed dexlansoprazole as the new active ingredient for DEXILANT.

It has been noted that conventional-release PPIs such as PREVACID may be unable to control acid secretion over a complete 24 hour period with a single daily oral dose.[21] Failure to obtain complete healing and/or symptom resolution after a standard course of PPI therapy is becoming more commonplace. For example, it has been estimated that 30% of GERD patients on PPI therapy will experience treatment failure.[22] Similarly, a return of symptoms in the latter part of the 24-hour treatment period has been widely reported with PPI treatment.[23]

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[19] *See* DEXILANT Approval Package, Clinical Pharmacology and Biopharmaceutics Review at 3. A 30 mg dose of lansoprazole contains approximately equal amounts of each enantiomer. Because the S-enantiomer is cleared more rapidly than dexlansoprazole, plasma exposure following administration of lansoprazole consists of at least 85% dexlansoprazole.

[20] *See* Tab 2, Katsuki, H., et al., *Determination of R(+)- and S(-)-lansoprazole using chiral stationary-phase liquid chromatography and their enantioselective pharmacokinetics in humans*, Pharm Res. (1996) 13: 611-5, 614, Table 2.

[21] *See* Tab 3, Tytgat, G.N., *Shortcomings of the first-generation proton pump inhibitors*, Eur. J. Gastroenterol. Hepatol. (2001) 13: S29-33, S30; *see also* Tab 4, Sachs, G., *et al*., *The pharmacology of the gastric acid pump: the H+,K+ ATPase*, Annu. Rev. Pharmacol. Toxicol. (1995) 35: 277-305, 295.

[22] *See* Tab 5, Fass, R., *Proton-pump inhibitor therapy in patients with gastrooesophageal reflux disease: putative mechanisms of failure*, Drugs (2007) 67: 1521-30, 1521.

[23] *See* Tab 3, Tytgat, *et al*., at 530.

This is in part because PPIs are capable of inhibiting active proton pumps only; inactive proton pumps are unaffected by PPI therapy.[24] Because only a fraction of gastric proton pumps are active at any given moment, if a gastric event occurs later in the day, previously inactive proton pumps can become activated. In addition, the effect on acid secretion can diminish over the dosing interval due to the regeneration of (H+, K+)-ATPase pumps within the gastric lining.[25] Thus, to counter sequential activations and later regeneration of proton pumps, DEXILANT employs a dual release formulation to prolong the plasma concentration-time profile of dexlansoprazole.

The early-releasing component of DEXILANT is based on a granule design similar to that found in PREVACID. Specifically, the early releasing granules in DEXILANT track the PK and pharmacodynamics ("PD") of PREVACID by releasing dexlansoprazole rapidly upon entry into the intestinal tract. Dexlansoprazole, once absorbed into systemic circulation, enters the gastric parietal cells and shuts down active proton pumps, blocking acid production within the first hours post-dose. The later releasing granules provide a second phase of drug release, to inhibit proton pumps that become active over the remainder of the dosing period.

B. Statutory and regulatory background

1. General standards for generic drug approvals

Under the Federal Food, Drug, and Cosmetic Act ("FDCA"), an ANDA is permitted to rely on FDA's previous finding of safety and effectiveness for the RLD. In order to rely on the prior finding , the applicant must show that the proposed product (1) has active ingredient(s), conditions of use, route of administration, dosage form, strength, and (with certain exceptions) labeling that are "the same as" the RLD, and (2) is bioequivalent to the RLD.[26]

Because two different manufacturers making the same drug product may use different formulations and components, and different manufacturing processes, the approved RLD and the proposed generic, even if they contain the same amount of active ingredient, have the potential to release or deliver different amounts of drug at different rates to the patient. Thus, studies are necessary to demonstrate bioequivalence to ensure that patients receive the same treatment whether they are dispensed the RLD or the

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[24] *See* id. at 531; Tab 4, Sachs, *et al.*, at 294.

[25] Tab 4, Sachs, *et al.*, at 295.

[26] *See* 21 USC 355(j)(2)(A); 21 CFR 314.94(a).

generic substitute.[27] Without bioequivalence there can be no assurance that products produced by different manufacturers are therapeutically equivalent.

2. Bioequivalence

A generic drug is considered bioequivalent to the RLD if "the rate and extent of absorption of the [generic] drug do not show a significant difference from the rate and extent of absorption of the [reference] drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses."[28] For a drug product that is intended to deliver the active ingredient systemically within the body, those parameters can be measured directly in the bloodstream.[29]

To establish bioequivalence, FDA generally requires that the 90% CI surrounding the ratios of the test drug to the reference drug for C_{max}, AUC_{0-t}, and AUC_{0-inf} (but not T_{max}) fit entirely within boundaries of 80% to 125%. Under this general approach, C_{max} is essentially used as a surrogate for the rate of absorption, and AUC serves as a surrogate for the extent of absorption.

3. Use of partial AUC parameters for multiphasic, modified-release products

FDA has acknowledged that there are certain drugs for which the statistical comparison of C_{max} and AUC as described above are insufficient to ensure that generic products will be as safe and effective as the RLD.[30] In its release of draft bioequivalence recommendations, announced on September 14, 2012,[31] the Agency published a model for the use of partial AUC metrics, which it requested for at least four different multiphasic, modified-release products.[32]

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[27] *See generally* 21 CFR 320.24.

[28] 21 USC 355(j)(8)(B)(i).

[29] *See* 21 CFR 320.24(b)(1)(i).

[30] *See, e.g.*, FDA Citizen Petition Response, Daytrana, Docket No. FDA-2012-P-0932 (Jan. 23, 2013) at 3 ("FDA recognizes that, under certain circumstances, it may be appropriate to use a partial AUC parameter to ensure comparable therapeutic effects.").

[31] 77 FR 56851.

[32] *See* Draft Guidance on Amphetamine Aspartate, Amphetamine Sulfate; Dextroamphetamine Saccharate; Dextroamphetamine Sulfate (Sept. 2012) ("Draft Guidance on Adderall XR"); Draft Guidance on Methylphenidate Hydrochloride Extended-Release Capsule (Sept. 2012) ("Draft Guidance on Metadate CD"); Draft Guidance on Methylphenidate Hydrochloride (Sept. 2012) ("Draft Guidance on Concerta");

In contrast, the Agency has generally rejected the use of partial AUC metrics for conventional, immediate-release dosage forms for oral administration. For such products, the potential effect of formulation on rate and extent of absorption can be captured by conventional metrics. Further, once absorbed, plasma concentration generally is governed not by formulation but by rate of elimination, which is independent of formulation. Accordingly, there must be an extraordinary rationale as to why additional measurements are necessary to establish bioequivalence for immediate-release drug products.[33] Similarly, FDA has not required partial AUC metrics for conventional extended-release drug products. For example, the Agency declined to require additional PK parameters for an extended-release oral capsule when the sponsor claimed the product exhibited a two-peak PK profile, but where the information in the labeling did not describe the plasma profile, and the effect was neither linked to the development of the product, or to a pharmacodynamic effect.[34]

Products that are approved and labeled for multiphasic release present entirely different circumstances.[35] In particular, FDA has required partial AUC analysis for products that contain dual-release technology, such as Metadate CD (methylphenidate HCl) extended-release capsules, Ritalin LA (methylphenidate HCl) extended-release capsules, Adderall XR (amphetamine sulfate; dextroamphetamine saccharate; dextroamphetamine sulfate) extended-release capsules, Focalin XR (dexmethylphenidate hydrochloride) extended-release capsules, and Ambien CR (zolpidem tartrate extended-release) tablets. FDA has also required the use of partial AUC metrics in cases where the RLD displays time-dependent localization of absorption within the gastrointestinal tract.[36] In citizen petition responses regarding these products, FDA has stated it will require as a condition of ANDA approval that the generic product be bioequivalent to the

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Draft Guidance on Focalin XR. Draft BE guidance documents are available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

[33] *See, e.g.*, FDA Citizen Petition Response, Silenor, Docket No. FDA-2011-P-0767 (Apr. 17, 2012); FDA Citizen Petition Response, Fentora, Docket Nos. FDA-2010-P-0383 and FDA-2010-P-0396 (Jan. 7, 2011).

[34] *See* FDA Citizen Petition Response, Cardizem CD, Docket No.98P-0145/CP1/SUP1 (Oct. 22 1999) at 9-10.

[35] *See generally* Briefing Package for the April 13, 2010 Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, *available at*: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm201700.htm.

[36] *See* FDA Citizen Petition Response, Asacol, Asacol HD and Pentasa, Docket Nos. FDA-2010-P-0111 and FDA-2008-P-0507 ("Asacol Petition Response") (Aug. 20, 2010); *see also, e.g.*, "Draft Guidance on Mesalamine" (Sept. 2012) ("Draft Guidance on Asacol"), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320002.pdf.

RLD at the 90% CI using appropriately tailored partial AUC metrics in addition to the conventional metrics, C_{max}, AUC_{0-t} and AUC_{0-inf}.[37]

II. ARGUMENT

A. DEXILANT is Approved and Labeled as a Multiphasic, Modified-Release Drug Product

DEXILANT is designed, approved and labeled as a dual-release drug product. This signature feature of the product is communicated in the labeling as follows:

> 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. Dexlansoprazole is eliminated with a half-life of approximately 1 to 2 hours in healthy subjects and in patients. . . . No accumulation of dexlansoprazole occurs after multiple, once daily doses of DEXILANT 30 mg or 60 mg, although mean AUC_t and C_{max} values of dexlansoprazole were slightly higher (less than 10%) on day 5 than on day 1.[38]

Under the Agency's prescription drug labeling regulations, 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.[39]

Also included in the approved labeling are clinical data showing improvement in the control of intragastric pH throughout the day following administration of a single morning dose of DEXILANT. As discussed in Section B, *infra*, the multiphasic modified-release formulation is intended to prolong intragastric pH control across the 24 hour dosing interval.[40] Meta-analyses have shown that the duration for which a PPI maintains intragastric pH at greater than 4, and the mean or median 24-hour pH levels,

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[37] *See* Metadate CD and Concerta Petition Response; Adderall Petition Response; *see also* Asacol Petition Response; FDA Citizen Petition Response, Ambien CR, Docket No. FDA-2007-P-0182 (Oct. 13, 2010).

[38] *See* Tab 1, DEXILANT Package Insert at 11 Description; *id.* at 12 Clinical Pharmacology.

[39] 21 CFR 201.57(c)(12)(ii) and (c)(13)(i)(C).

[40] *See* Tab 1, DEXILANT Package Insert at 12.2 Clinical Pharmacology (Pharmacodynamics), Table 3.

are predictors of esophageal healing and provide a model for evaluating acid-suppression therapies.[41] More recently, Katz *et al.* presented data from a prospective, randomized controlled trial confirming an association between acid control (defined as intragastric pH > 4) and healing in patients with moderate to severe erosive esophagitis (grades C–D, as defined by the Los Angeles Classification System).[42] Finally, published literature discussing PK/PD modeling support the relationship between the sustained plasma levels achieved with DEXILANT and the duration and degree of intragastric pH control.[43]

As with the product description, the pharmacodynamic effect of the drug is clearly communicated in the labeling. Physicians rely on this information to make prescribing decisions and patients may discuss these distinctive aspects of the product with their healthcare provider. Thus, the dual-release formulation is an important and significant feature of the product, and must be replicated in any product that purports to be "the same as" DEXILANT.

For products that are approved and labeled for multiphasic, modified-release, the Agency has now consistently recognized the need for statistical analysis of partial AUC to ensure that proposed generics replicate the basic design of the RLD. In doing so, the Agency highlighted that these products are expressly labeled for biphasic release.[44] The additional metrics allow the Agency to analyze the plasma concentration-time profile of the proposed generic relative to the RLD in time delimited (partial) segments. These segments approximate the (two) discrete phases of release found in these types of products. That is, embedded within each of these products is a discrete component that is comparable to a stand-alone, immediate release drug product. For example, in reference to Concerta and Metadate CD, the Agency observed:

> [The MR methylphenidate products] contain IR and ER components in their formulations and exhibit biphasic absorption characteristics, which

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[41] *See* Tab 6, Bell, N.J.V., *et al*., *Appropriate acid suppression for the management of gastro-oesophageal reflux disease*, Digestion (1992) 51: 59-67, 64; Tab 7, Yuan, Y., *et al*., Gastroenterology (2007) 132: A489 (Abstract). The shape of the intragastric pH curve is not as relevant to successful acid control as the time the pH is above 4. Parietal cell acid secretion is affected by circadian factors as well as intragastric stimulation. Acid secretion is highest during the evening and overnight hours. *See* Tab 8, Moore, J.G., and Englert, E., Nature (1970) 226: 1261-2; Tab 9, Peghini, P.L., *et al*., Am J. Gastroent. (1998) 93: 763-7, 761.

[42] Tab 10, Katz, P.O., *et al*., *Relationship between intragastric acid control and healing status in the treatment of moderate to severe erosive oesophagitis*, Aliment. Pharmacol. Ther. (2007) 25: 617-28, 624.

[43] Tab 11, Vakily, M., *et al*., *Pharmacokinetics and pharmacodynamics of a known active PPI with a novel Dual Delayed Release technology, dexlansoprazole MR: a combined analysis of randomized controlled clinical trials*, Curr. Med. Res. Opin. (2009) 25: 627-638, 634.

[44] Draft Guidance on Adderall XR at 2; Draft Guidance on Metadate CD at 2-3; Draft Guidance on Concerta at 2; Draft Guidance on Focalin XR at 3.

> results in rapid initial absorption similar to IR methylphenidate, followed by an extended release of methylphenidate. Thus, in the first IR phase, Concerta and Metadate CD are designed to provide initial plasma concentrations comparable to IR methylphenidate.[45]

Similarly, for Adderall XR, the Agency found that the product is fundamentally "designed to mimic the drug release of two Adderall [immediate release (IR) mixed amphetamine] tablet formulations taken four hours apart."[46]

To ensure that a proposed generic likewise contains the embedded immediate release component, along with a component to provide a second phase of release, FDA has made partial AUC metrics an essential part of the analysis. As the Agency explained in the Adderall XR petition response:

> We think it is important to use partial AUC for some specialized dosage forms, because [the traditional] criteria . . . may not be adequate for certain drugs formulated as multiphasic [modified-release] products . . . . It is important to carefully select the appropriate partial AUC sampling times for a multiphasic [modified-release] formulation because . . . T_{max} associated with the highest plasma concentration may occur as drug is released from the [delayed-release] component of the formulation . . . . Thus, the traditional BE metrics . . . will not provide information on the initial onset of activity.[47]

In short, because the dosage forms in these types of products (1) contain immediate-release and delayed-release components, (2) are designed to achieve both rapid onset of activity and sustained activity throughout the day, and (3) do not show unusual accumulation at steady-state, an additional metric is needed to ensure true therapeutic equivalence.[48]

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[45] Metadate CD and Concerta Petition Response at 8.

[46] *Id.*

[47] Adderall XR Petition Response at 8-9.

[48] *See id.* The generality of this standard is further illustrated in FDA's model for Quality by Design ("QbD") for ANDAs for modified-release dosage forms where the need for partial AUC metrics is implicitly and explicitly articulated. The hypothetical example RLD in the model is a dual-release product composed of both an immediate release ("IR") and an extended release ("ER") component in which FDA reports, according to the product label, "the IR phase achieves plasma concentrations comparable to the IR product . . . through the first two hours for rapid onset of the therapeutic effect. The ER phase sustains plasma concentrations of the drug through 24 hours for maintenance of the therapeutic effect." The RLD exhibits biphasic kinetics with a first peak occurring at 1-2 hours and a second peak at 4-8 hours. According to FDA, the pivotal BE study for this product requires that the 90% confidence interval meet the

DEXILANT contains the same type of dual-release mechanism, with labeling that recognizes the bi-modal release profile and biphasic kinetics of the product. According to the approved labeling, DEXILANT showed a prolonged effect on 24-hour intragastric pH, an important pharmacodynamic measure in the PPI class. DEXILANT also showed statistically significant effects over placebo in percentage of 24-hour heartburn-free periods in patients with healed EE and in patients with symptomatic non-erosive GERD.[49] As with other dual-release products, traditional BE metrics are not adequate to ensure bioequivalence for proposed generic versions of DEXILANT.

B. Proposed Generics to DEXILANT Must be Bioequivalent at Each Phase of Drug Release to be Considered Therapeutically Equivalent to DEXILANT

DEXILANT is designed to prolong the plasma concentration-time profile of dexlansoprazole and extend acid suppression with once-daily dosing. As discussed, DEXILANT relies on dual delayed-release technology to provide a specific PK profile. The safety and effectiveness of DEXILANT is based on the product's dual-release profile, which is designed to maximize exposure to dexlansoprazole over the dosing interval. There can be no assurance that a generic product would achieve the same clinical results as DEXILANT unless the generic is bioequivalent to DEXILANT at each phase of release.

Pharmacologic therapy with PPIs provides potent acid suppression and is associated with well-established efficacy in treating acid-related gastroesophageal diseases.[50] However, conventional single-release PPIs may be unable to control acid secretion over a complete 24 hour period with a single daily oral dose.[51] Failure to obtain complete healing and/or symptom resolution after a standard course of PPI therapy is becoming commonplace, and return of symptoms in the latter part of the 24-hour

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bioequivalence limit of 80-125% for AUC_{0-2}, AUC_{0-24}, in addition to AUC_{0-inf}, and C_{max}. *See* Quality by Design for ANDAs: An example for Modified Release Dosage Forms at 7, 27 (Dec. 2011), *available at* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM286595.pdf.

[49] *See* Tab 1, DEXILANT Package Insert at 12.2 Clinical Pharmacology; *id.* at 14.2 and 14.3 Clinical Studies.

[50] Tab 4. Sachs, *et al.*, at 278. The chief function of PPIs is to inhibit the secretion of acid to the stomach. *See* Tab 1, DEXILANT Package Insert at 12.1 Mechanism of Action.

[51] *See* Tab 3, Tytgat, *et al.*, at 531.

treatment period often occurs with PPI treatment.[52] For example, it has been estimated that 30% of GERD patients on PPI therapy will experience treatment failure.[53]

DEXILANT was designed to maximize the duration of exposure to a proven PPI over a once-daily dosing interval. The safety and effectiveness data in support of the product reflect the increased exposure allowed by the dual-release dosing format. The timing of the two release phases is rooted in the biology of proton pump inhibition. Gastric acid production is a function of the parietal cells that reside within the gastric pits that line the stomach wall. Dexlansoprazole enters the parietal cells via systemic circulation, then binds to and shuts down activated proton pumps.[54] However, if an intragastric event occurs later in the day, in the absence of therapeutic levels of PPI, proton pumps that were not previously active, or have been newly generated,[55] become activated -- causing acid production to increase.

Further, because the plasma half-life of a conventional, single-release PPI is between 1 and 2 hours, once the maximal inhibition of active pumps has been achieved, newly synthesized or activated pumps will not be inhibited 3 hours post-dose because therapeutic levels of drug will not be present in the plasma.[56] Sachs *et al.*, among others, therefore proposed that with twice-a-day ("BID") dosing, inhibition will be both rapid and longer lasting.[57]

To gain a more complete understanding, Takeda performed a clinical study to assess the difference in pH control between QD and BID dosing of PREVACID. The study compared the pH control of lansoprazole 30 mg QD (the highest approved dose) and 15 mg BID, and the pH control of lansoprazole 60 mg QD and 30 mg BID. The study showed no statistically significant differences in percent time pH > 4 between the

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[52] *See id.*

[53] *See* Tab 5, Fass, at 1521.

[54] *See* Tab 4, Sachs, *et al.*, at 290. Normally, proton pumps are in an inactive state and do not produce acid. Proton pumps that are not active are unaffected by PPI therapy. PPIs react only with the pumps that are present in the secretory canaliculus. This is because only the pumps of the canalicular membrane are actively forming hydrochloric acid, and acidification of the PPI is necessary to convert the molecule to the sulfonamide moiety that binds to, and inhibits, the gastric pump. When an intragastric event occurs such as when food is introduced into the system, some but not all parietal (H^+, K^+)-ATPase pumps become active. Activated proton pumps are effectively targeted through conventional PPI therapy.

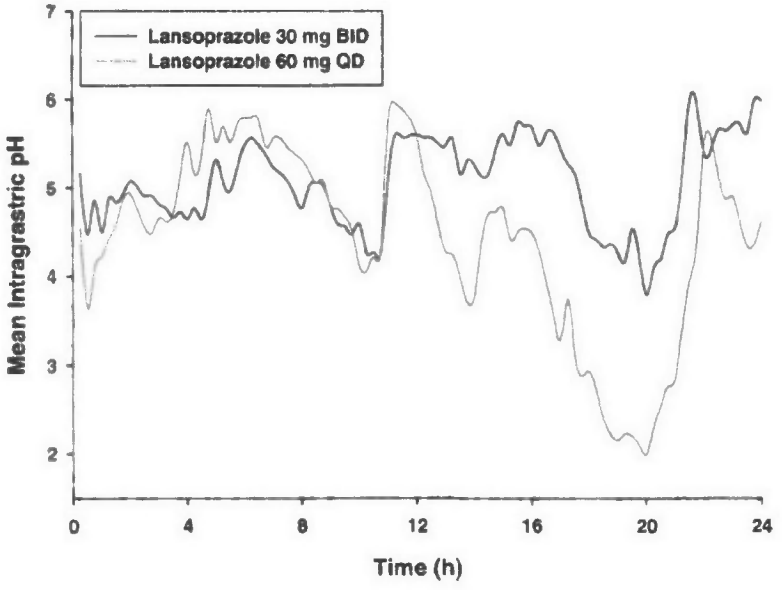
[55] *See id.* at 295. Approximately 25% of the total number of available pumps are replaced with newly-synthesized pumps within a 24-hour period. Therefore, on once-a-day dosing, significant amounts of newly-synthesized pumps that have not been exposed to drug will be present 24 hours after dosing.

[56] *See id.*

[57] *See id.* at 296.

30 mg QD and the 15 mg BID regimens; however, percent time pH > 4 was statistically different and greater for the 30 mg BID regimen as compared to the 60 mg QD regimen for the entire 24 hour post-dose period and also for the nighttime hours.[58] The study showed that providing daily doses of lansoprazole higher than the approved 30 mg dose – and giving those doses twice over the course of the day (*e.g.*, every 12 hours) – may produce significantly improved 24-hour pH control (Figure 1).

Figure 1 The 24-hour Intragastric pH Profile Following Administration of PREVACID (Lansoprazole) 60 mg QD and 30 mg BID



Having observed an improvement in percent time pH > 4 between PREVACID 60 mg QD and 30 mg BID, Takeda conducted extensive research and, ultimately, developed DEXILANT to approximate the effect of two single doses of PREVACID at an interval that would maximize drug exposure. Like PREVACID, the first release phase is intended to shut down proton pumps that are active or become active in the first several hours post dose. The second phase of release inhibits proton pumps that become active later in the dosing interval. DEXILANT's dual-release design therefore prolongs the plasma concentration-time profile of dexlansoprazole to provide an extended duration of acid suppression. Specifically, 30 mg of DEXILANT would be expected to provide a

[58] Clinical Study Report for M93-006, "Dose Response Evaluation of Multiple Doses of Lansoprazole (ABT-006) Using 24-Hour Determinations of pH." NDA 20-406, Supplement 002, Amendment 001 (Aug. 1995).

comparable pharmacodynamic effect as a 15 mg dose of PREVACID followed by a 45 mg dose of PREVACID given approximately 3-5 hours apart.[59]

Furthermore, Takeda designed DEXILANT to deliver its second phase of drug release at a specific distal location within the small intestine, prior to entrance into the colon.[60] Because of gastric transit time and GI physiology, a dual-release product with a second phase that releases too late – *i.e.*, after the formulation has passed the ileocecal junction – would blunt the effect of the second phase. In contrast, if the second release occurs too quickly, at a location that is too proximal within the small intestine, the BID-like effect would not be achieved. DEXILANT QD therefore approximates PREVACID BID by promoting absorption of the first delayed-release granule in the proximal small intestine and delaying absorption of the second granule for a second pulsed-release as late as possible before the granules reach the colon.

In clinical studies, DEXILANT showed improved pH control versus PREVACID QD. As reported in the product labeling, DEXILANT 60 mg maintains statistically significant intragastric pH > 4 for 71% (17 hours) of the 24-hour post-dosing period as compared to 60% (14 hours) following administration of PREVACID 30 mg. The improved 24-hour intragastric pH profile with DEXILANT may be attributed both to a greater daily dose as compared to PREVACID 30 mg QD, and to the change in the specific concentration-time profile after oral administration. The PK profile of DEXILANT provides mean drug concentrations between 0 to 2 hours post-dose that are comparable to PREVACID, and substantially greater circulating dexlansoprazole concentrations between 6 and 18 hours post-dose that are due to the second release of drug.

The timing of the dual release formulation is central to the safety and efficacy profile of DEXILANT. A proposed drug product that fails to provide a second phase of release in the distal region of the small intestine, prior to entry in the colon, cannot be expected to perform the same, clinically, as DEXILANT. In short, a generic that is not shown to be bioequivalent at both the initial phase of release, and the second delayed phase of release, cannot be said to be therapeutically equivalent to DEXILANT.

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[59] Because half of the lansoprazole contained in PREVACID is the *S*-enantiomer, which is rapidly cleared from the plasma, the circulating plasma component following administration of PREVACID is predominantly dexlansoprazole and approximates the plasma concentrations of dexlansoprazole following administration of DEXILANT at half the nominal strength. In other words, a 30 mg dose of DEXILANT contains as much dexlansoprazole as 60 mg of PREVACID.

[60] Takeda has determined that the bioavailability of lansoprazole in the colon is approximately 30% of the bioavailability when released in the small intestine. The same is believed to be the case for dexlansoprazole which, like lansoprazole, is primarily absorbed via passive diffusion across the intestinal lining.

C. A Partial AUC Metric Must be Established to Show Bioequivalence to DEXILANT

FDA has determined that for multiphasic, modified-release products, analysis of partial AUC is required when, in addition to the factors discussed above, the observed C_{max} reflects only the second phase of release. In such cases, traditional BE metrics cannot provide information on the initial phase of release.[61]

So too here. For DEXILANT the Agency cannot rely on observations with respect to C_{max} or T_{max} as a basis for concluding that a proposed generic will have the same onset of activity. Peak concentration of dexlansoprazole in systemic circulation, or C_{max}, is a function of the second phase of release.[62] C_{max} therefore cannot measure the rate and extent of absorption of the PREVACID-like first phase of release. In other words, C_{max} is a feature of delayed absorption from the late-releasing granule and does not capture onset of activity of the early-releasing granule.

Further, as with Adderall XR, Concerta and Metadate CD, the T_{max} for DEXILANT does not occur until drug from the second type of granule has begun to be released. Thus, T_{max} does not reflect the first phase of release, let alone permit it to be analyzed on a statistical basis. As a result, a partial AUC metric is needed to assess the rate and extent of absorption of the early-release component of a proposed generic product.

The specific and most appropriate partial AUC parameters are aptly illustrated by DEXILANT's PK profile versus QD PREVACID. As a result of the two distinct releases of drug in a single dose, the PK profile of dexlansoprazole following the administration of DEXILANT is characterized by a plasma concentration-time profile with 2 distinct peaks (Figure 2). The first peak is similar to the plasma concentration-time profile observed with a single dose of PREVACID (lansoprazole) 30 mg, with a C_{max} approximately 2 hours after administration. The drug that is released from 0 to 2 hours post-dose (area under the curve from time 0 to 2 hours post-dose (AUC_{0-2h})) occurs in the proximal small intestine and inhibits the pumps that are active immediately after dose. The second release of drug occurs in the distal part of the small intestine, with residual release occurring in the colon (approximately 4-5 hours after administration) and provides extended plasma dexlansoprazole concentrations (AUC from 2 to 10 hours post-dose (AUC_{2-10h})) to inhibit the pumps that are newly formed or newly activated later in

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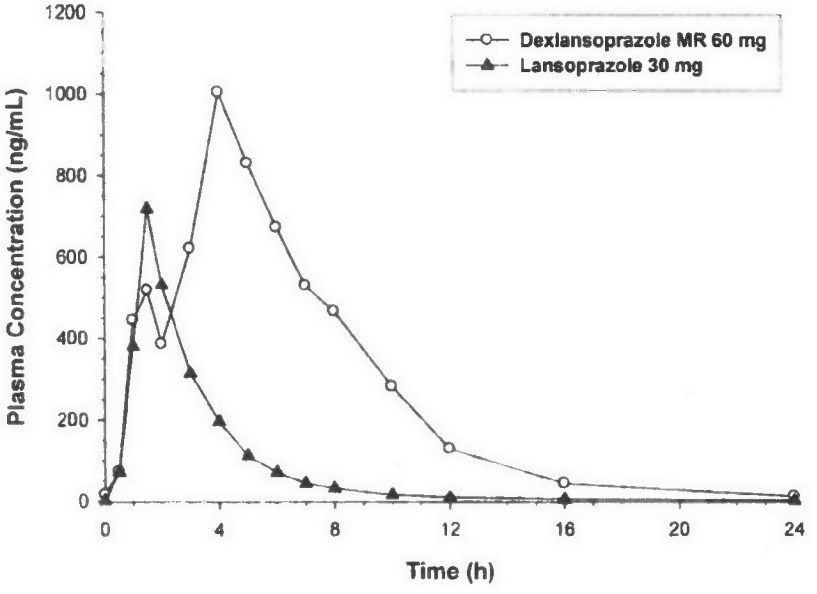
[61] *See, e.g.*, Adderall XR Petition Response at 8-9.

[62] *See* Tab 1, DEXILANT Package Insert at 12.3 Pharmacokinetics.

the day. These partial AUC metrics are directly derived from the PK profile as illustrated by Figure 2.

Figure 2 Plasma Concentration-Time Plots for DEXILANT QD (Dexlansoprazole MR 60 mg) and PREVACID QD (Lansoprazole 30 mg)



Based on the well-defined dual release profile of DEXILANT, with the second phase of release designed to account for gastric transit time, FDA must require that bioequivalence is demonstrated using $pAUC_{0\text{-}2h}$, $pAUC_{2\text{-}10h}$, in addition to conventional metrics. These parameters accurately capture the biphasic PK that is clearly illustrated in the product labeling. As discussed above, biphasic release is a critical feature of the product, and physicians rely on this information to make prescribing decisions. Accordingly, a generic version of DEXILANT must be bioequivalent with regard to each phase of release. The additional metrics, $pAUC_{0\text{-}2h}$ and $pAUC_{2\text{-}10h}$, are essential to ensure that a generic can replicate the timing and extent of the dual-release of DEXILANT and therefore that it will provide equivalent exposure and pharmacological response.

III. CONCLUSION

For the above stated reasons, FDA must refrain from approving any ANDA referencing DEXILANT unless the proposed generic drug product has been shown to be bioequivalent to DEXILANT using a partial AUC metric designed to ensure the same dual-release profile as that shown in the approved labeling for DEXILANT.

ENVIRONMENTAL IMPACT

The actions requested in this Citizen Petition are subject to categorical exclusion under 21 CFR 25.31.

ECONOMIC IMPACT

Information on the economic impact of this Petition will be provided at the request of the Commissioner of Food and Drugs.

CERTIFICATION

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. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: June 22, 2012. 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 those payments from the following persons or organizations: None, other than my compensation as an employee of Takeda. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

[Signature page to follow]

Respectfully submitted,

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Enclosures

Cc: Gregory P. Geba, M.D., M.P.H.
Director
Office of Generic Drugs