DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

AUG 18 2010

Greg J. Kricorian, M.D.
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International Headquarters
3300 Hyland Avenue
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Re: Docket No. FDA-2006-P-0009

Dear Dr. Kricorian:

This letter responds to your citizen petition received by the Food and Drug Administration (FDA or the Agency) on September 22, 2006 (Petition).[1] The petition requests that FDA refrain from approving any abbreviated new drug application (ANDA) that relies on Diastat (diazepam rectal gel) 5 milligram (mg)/milliliter (mL), 10 mg/2 mL, 15 mg/3 mL, or 20 mg/4 mL as the reference listed drug (RLD). Alternatively, if the Agency permits an applicant to reference these drug products, you argue that we should require the applicant to submit a new drug application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) because, you assert, significant labeling changes would be required for the safe use of the new product.

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

In a related petition submitted to FDA by Lachman Consultant Services, Inc. (Lachman), on May 15, 2006, Lachman requested that FDA determine whether Diastat (diazepam rectal gel) 5 mg/mL, 10 mg/2 mL, 15 mg/3 mL, or 20 mg/4 mL was withdrawn from the market for reasons of safety or efficacy.[2] FDA has determined that these drug products were not removed for reasons of safety or efficacy and we are publishing our decision in the *Federal Register*.[3]

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[1] This citizen petition was originally assigned docket number 2006P-0392/CP1. The number was changed to FDA-2006-P-0009 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[2] Before FDA can approve an ANDA referencing a drug product that is no longer marketed, the Agency must first determine whether that drug product was removed from the market for reasons of safety or efficacy (21 CFR 314.161(a)(1)). An ANDA that refers to a drug product that is no longer marketed must be accompanied by a citizen petition to the Agency requesting that the Agency make such a determination (21 CFR 314.122(a)). The Agency then determines whether the particular drug product was removed from the market for reasons of safety or efficacy and publishes that determination in the *Federal Register*.

[3] 75 FR 51080, August 18, 2010.

FDA-2006-P-0009_ PDN

I. BACKGROUND

A. Diastat

Valeant Pharmaceuticals International (Valeant) is the application holder for Diastat (diazepam rectal gel), which was approved by the Agency on July 29, 1997 (NDA 20-648).[4] Diastat (diazepam rectal gel) contains a gel formulation of diazepam intended for rectal administration for the management of selected, refractory patients with epilepsy, on stable regimens of antiepileptic drugs, who require intermittent use of diazepam to control bouts of increased seizure activity. This drug product was originally co-packaged in five fixed-dose syringes: 2.5 mg/.05 mL, 5 mg/mL, 10mg/2 mL, 15 mg/3 mL, and 20 mg/4 mL.

On September 15, 2005, FDA approved a supplement to the original NDA (NDA 20-648/S008) for a new delivery system for the same formulation of diazepam rectal gel in Diastat. The drug product in the new delivery system is marketed under the trade name Diastat AcuDial. It includes a plastic applicator with a flexible, molded tip in two different lengths, and is available as a 10 mg delivery system and a 20 mg delivery system. The available doses from the 10 mg delivery system are 5 mg, 7.5 mg, and 10 mg. The available doses from the 20 mg delivery system are 12.5 mg, 15 mg, 17.5 mg, and 20 mg. Diastat AcuDial has a syringe with a locking mechanism that allows pharmacists to set the prescribed dose and lock that dose into place.

The approval and marketing of Diastat AcuDial was accompanied by the removal from the market of the original fixed-dose syringe formulation[5] and the implementation of a risk management program (RMP). The RMP was instituted to educate and train pharmacists, prescribers, caregivers, and patients on using the new AcuDial delivery system in a safe and effective manner.

B. The Legal and Regulatory Background for Generic Drug Products

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) established two abbreviated pathways for drug product approval: the pathway described in section 505(j) of the Act and the pathway described in section 505(b)(2) of the Act. Section 505(j) describes the ANDA approval process. To obtain approval of an ANDA, an applicant does not provide independent evidence of safety and effectiveness but, instead, relies on the finding of safety and effectiveness for a drug that has been previously approved. An ANDA must identify a listed drug on which it seeks to rely and, with limited exceptions, an ANDA must contain the same active ingredient,

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[4] Xcel Pharmaceuticals (Xcel) was the original applicant for Diastat (diazepam rectal gel). Valeant purchased Xcel in 2005.

[5] It is important to note that the original Diastat delivery system in the 2.5 mg/.05 mL fixed-dose syringe remains on the market.

conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD (see, e.g., 21 CFR 314.94(a)(4)-(a)(8)). In addition, an ANDA applicant must establish that its drug is bioequivalent to the RLD.[6]

The Act also requires that an ANDA contain "information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the Act] or because the new drug and the listed drug are produced or distributed by different manufacturers" (section 505(j)(2)(A)(v) of the Act). A parallel provision appears in section 505(j)(4)(G) of the Act.[7]

Similarly, the regulations at 21 CFR 314.94(a)(8)(iv) require the following:

> Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the [generic] drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 [21 CFR 314.93] or because the drug product and the reference listed drug are produced or distributed by different manufacturers.

Section 314.94(a)(8)(iv) sets forth examples of permissible differences in labeling that may result because the generic drug product and reference listed drug are produced or distributed by different manufacturers. These differences include the following:

> . . . differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the [A]ct.[8]

Section 505(b)(2) of the Act was also enacted as part of the Hatch-Waxman Amendments. A 505(b)(2) application is an NDA that relies for approval, at least in part, on data and information that are not owned by the applicant and to which the applicant

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[6] A drug described in an ANDA 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, 21 U.S.C. 355(j)(8)(B)(i); see also 21 CFR 320.1(e) and 320.23(b).

[7] Section 505(j)(4)(G) of the Act provides that FDA must approve an ANDA unless, among other things, the "information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for [the reference listed drug] except for changes required because of differences approved under [an ANDA suitability petition] or because the drug and the listed drug are produced or distributed by different manufacturers."

[8] We note that, due to a series of amendments to the Act, the reference in § 314.94(a)(8)(iv) to section 505(j)(4)(D) of the Act corresponds to current section 505(j)(5)(F) of the Act.

does not have a right of reference.[9] The requirements for applications approved using the section 505(b)(2) pathway differ from the requirements for ANDA approval under section 505(j) of the Act. Although both types of applications may include comparisons to and reliance on a listed drug, with very limited exceptions an ANDA submitted under 505(j) must contain evidence that the proposed drug is therapeutically equivalent and bioequivalent to the RLD and that the proposed drug labeling is essentially the same as that of the approved listed drug. In contrast, a 505(b)(2) application may be, but is not required to be, therapeutically equivalent or bioequivalent to the listed drug it references or to have the same labeling as that listed drug. A 505(b)(2) application, like any drug approved in an NDA, must contain information adequate to show that the drug is safe and effective. The Agency may approve 505(b)(2) applications that rely on published literature or on the Agency's finding of safety and effectiveness for another listed drug product, provided that such reliance is scientifically justified and the 505(b)(2) applicant complies with the applicable statutory requirements regarding patent certification. A 505(b)(2) applicant must also submit data necessary to support the safety and effectiveness of any aspects of the proposed drug product that represent modifications to or changes from the listed drug on which it relies.[10]

II. DISCUSSION

A. FDA May Approve ANDAs for Diazepam Rectal Gel Referencing the Original Fixed-Dose Delivery System, and the Fixed-Dose Delivery System Can Be Marketed Simultaneously with the Diastat AcuDial Delivery System

You request that FDA refrain from approving any ANDA that relies on Diastat (diazepam rectal gel) 5 mg/mL, 10 mg/2 mL, 15 mg/3 mL, or 20 mg/4 mL as the RLD. In your petition, you state that having the Diastat AcuDial product and the fixed-dose syringe diazepam rectal gel on the market at the same time will cause confusion and potentially cause medication errors, thereby affecting the safe and effective use of these drug products (Petition at 3).

As mentioned above, we have determined in a response to a separate citizen petition submitted by Lachman that the original formulation of Diastat using the fixed-dose delivery system was not withdrawn from the market for reasons of safety or efficacy. As such, the Agency will continue to list Diastat (diazepam rectal gel) 5 mg/mL, 10 mg/2 mL, 15 mg/3 mL, or 20 mg/4 mL, in the "Discontinued Drug Product List" section of the Orange Book, which delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. As a result, the Agency will accept ANDAs that refer to Diastat (diazepam rectal gel) 5 mg/mL, 10

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[9] A 505(b)(2) application is an NDA described in section 505(b)(2) of the Act. It is submitted under section 505(b)(1) of the Act and approved under section 505(c) of the Act.

[10] See the FDA draft guidance for industry on *Applications Covered by Section 505(b)(2)* (64 FR 68697, December 8, 1999), available at http://www.fda.gov/cder/guidance/index.htm; see also October 14, 2003, letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Katherine Sanzo, et al., Docket Nos. 2001P-0323, 2002P-0447, and 2003P-0408.

mg/2 mL, 15 mg/3 mL, or 20 mg/4 mL, and such ANDAs may be approved by the Agency if all other legal and regulatory requirements for the approval of ANDAs are met.

You claim that FDA urged Valeant to withdraw the Diastat fixed-dose syringe from the market to avoid any risk of confusion and medication errors that would result from having both the Diastat fixed-dose and Diastat AcuDial products on the market at the same time (Petition at 1). You state that FDA required Valeant to implement an RMP that included the extensive education and training of pharmacists, prescribers, caregivers, and patients to ensure the safe and effective use of Diastat AcuDial (Petition at 3). You state that the RMP described the importance of the proper administration of the drug product, the differences between the fixed-dose syringe and the AcuDial product, and the features of the new delivery system (Petition at 3). In addition to implementing the RMP, the labeling required changes to give detailed instructions on how to dispense and use Diastat AcuDial with the new delivery system (Petition at 3). Finally, you state that the RMP reflected the FDA and Valeant shared view that marketing of both the Diastat AcuDial and fixed-dose products with duplicative doses would create the risk of confusion and medication errors that could not be adequately mitigated by education and training (Petition at 3). You emphasize that Valeant began to remove the fixed-dose Diastat product from the market 5 weeks before the launch of the Diastat AcuDial product to avoid having an overlap of both products on the market at the same time (Petition at 4).

We disagree with your assertion that FDA urged Valeant to remove the fixed-dose Diastat product from the market to avoid any overlap with the new Diastat AcuDial delivery system and prevent any confusion between the two products. In your comment of November 17, 2006, you refer to our March 2005 approvable letter in which FDA recommended that the duration of the overlap in the marketing of both products be as short as possible. Although the Agency was concerned about both Diastat products being marketed at the same time because of potential confusion, we did not require the removal of the fixed-dose syringe product. If both products were to be marketed simultaneously, we recommended that Valeant implement an aggressive educational program to inform the relevant parties about the existence of both delivery systems in order to avoid confusion. It is important to note that Valeant voluntarily made the decision to remove the fixed-dose Diastat product from the market around the time of the introduction of AcuDial. FDA's discussions with Valeant about removing the fixed-dose Diastat product from the market were a direct result of Valeant's decision to remove the product from the market. FDA discussed with Valeant the optimal timing of withdrawing the fixed-dose product from the market rather than the absolute necessity of removing the product from the market for reasons of patient safety. FDA may not have required the withdrawal of the fixed-dose products if Valeant had proposed to market them simultaneously with the AcuDial product. However, given the pre-existing decision by Valeant to discontinue the duplicated fixed-dose product, FDA thought it was prudent to suggest that the timing of this withdrawal coincide with the introduction of Diastat AcuDial.

The introduction of the novel and complicated AcuDial delivery system necessitated a rapid education and awareness program for prescribers, pharmacists, and patients that would be optimally effective if the new AcuDial product were immediately available nationwide. The new handling procedure for the AcuDial product could be forgotten if not used immediately after training. Thus, the presence of a potentially large amount of phased-out fixed-dose product at pharmacies would slow the appearance of the AcuDial delivery system and potentially interfere with the effectiveness of the awareness/education program. However, this would arguably no longer be a problem once the AcuDial system was available to all pharmacies (and familiar to prescribers, pharmacists, and patients). Because the Diastat AcuDial product has been on the market since 2005, we believe prescribers, pharmacists, and patients have been thoroughly educated on the appropriate use of the AcuDial delivery system. Therefore, the presence on the market of both the fixed-dose and AcuDial products at the present time would not interfere with the educational processes for using Diastat AcuDial and does not present an ongoing reason for concern about patient safety.

The RMP was designed to minimize medication errors that may result from incorrect dosing due to inaccurate dose dial and lock-in of the prescribed dose in the AcuDial delivery device, and to ensure proper disposal of the unused diazepam gel after administration of the dose. The RMP makes no mention of potential medication errors that would result from the presence on the market of both Diastat AcuDial and fixed-dose products. Additionally, a generic version of the fixed-dose diazepam rectal gel delivers the total drug with a single dose administration with no unused diazepam gel left in the syringe. Therefore, the RMP for Diastat AcuDial is not relevant to the marketing and use of generic versions of Diastat.

It is important to remember that the RMP was instituted because of the complexity of the AcuDial product. In fact, the complexity has led to a number of instances of patients receiving the wrong dose because the device was not properly dialed and locked. Although you argue that the simultaneous presence of both the fixed-dose Diastat product and the Diastat AcuDial product may cause confusion among pharmacists, patients, and caregivers trained to use one or the other product, Valeant nevertheless is currently marketing simultaneously both a fixed-dose 2.5 mg Diastat and the AcuDial product. It could be argued that for some caregivers and patients the simplicity of fixed-dose preparations might outweigh the advantage of the nuanced dosing of the AcuDial product, which involves the potential for error at each step of setting, locking, and verifying the dose. Thus, for these caregivers and patients, the presence of both the fixed-dose product and the AcuDial product in the marketplace would be an advantage.

B. Sponsors Referencing the Fixed-Dose Diastat Product Are Not Required to Submit an NDA Under 505(b)(2) of the Act

In your petition, you suggest that if a fixed-dose product were to come onto the market, the risks of confusion and medication errors would have to be addressed in the product's labeling, as well as by educating and training doctors, pharmacists, caregivers, and patients. This would result in extensive changes from the labeling that was available in

2005 for the fixed-dose Diastat products, and you claim that such changes are not permitted by the regulations governing generic drug products. As a result, you argue that a sponsor seeking to rely on the fixed-dose Diastat product must submit an NDA under section 505(b)(2) of the Act because such a drug product would require significant labeling changes that would make it ineligible for approval as an ANDA.

We disagree that the approval of an ANDA for a fixed-dose diazepam rectal gel referencing the withdrawn Diastat fixed-dose product would increase the risk for confusion and medication errors. The fixed-dose product is a simple to use, single dose syringe that requires no manipulation to lock-in delivery of the desired dose. This is in contrast to Diastat AcuDial, which requires that the pharmacist accurately dial and lock in the prescribed dose in the delivery system, which can deliver different doses. For this reason, special training of health care providers, pharmacists, and caregivers is needed for Diastat AcuDial, but not for the fixed-dose products. Additionally, there is no evidence that the fixed-dose products were withdrawn from the market for safety reasons (see 75 FR 51080, August 18, 2010). Valeant has not provided any data to support the potential for confusion with the concurrent availability on the market of Diastat AcuDial and generic versions of the fixed-dose Diastat product.[11] Nevertheless, the Agency will monitor reports of adverse events submitted under FDA's safety information and adverse event reporting program (MedWatch), and will take corrective action if there are any safety concerns associated with the simultaneous marketing of the fixed-dose and the AcuDial products.

With respect to labeling changes, we have determined that the product labeling for a generic product referencing the fixed-dose Diastat does not require the changes you suggested in your petition. Any labeling changes for a drug product referencing the fixed-dose Diastat product are well within the differences allowable by the statute and our own regulations. Consequently, your request that FDA require applicants referencing the fixed-dose Diastat product to submit an NDA under to section 505(b)(2) of the Act is denied.

III. CONCLUSION

We have reviewed the petition and other relevant information available to us. For the reasons discussed above, your petition requesting that FDA refrain from approving any ANDA that relies on Diastat (diazepam rectal gel) 5 mg/mL, 10 mg/2 mL, 15 mg/3 mL, or 20 mg/4 mL as the RLD is denied. The fixed-dose Diastat (diazepam rectal gel) was not removed from the market for reasons of safety or efficacy, nor do we believe that the marketing of both the fixed-dose product and Diastat AcuDial would pose any safety concerns due to a risk of confusion. We are also denying your request that an applicant referencing the fixed-dose Diastat product submit an NDA under section 505(b)(2) of the

[11] We note that, because the ANDA products would rely on the Diastat fixed-dose rather than Diastat AcuDial, it would not be expected that the generic product would be automatically substituted for Diastat AcuDial if the patient has received a prescription for the latter product.

Act, as opposed to submitting an ANDA under section 505(j) of the Act. Any fixed-dose product referencing Diastat (diazepam rectal gel) will not require your suggested labeling changes or any other labeling change that is inconsistent with an ANDA approval. Therefore, such applications can be approved as ANDAs.

Sincerely,

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