

VALEANT
Pharmaceuticals International

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August 7, 2006

BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

**Re: Docket No. 2006P-0209/CP1
Comments of Valeant Pharmaceuticals International**

Dear Sir or Madam:

Valeant Pharmaceuticals International ("Valeant") submits the following comments to the above-referenced citizen petition, submitted May 15, 2006, by Lachman Consultant Services, Inc. ("Lachman").

The Lachman petition asks FDA to determine whether Valeant withdrew Diastat® (diazepam rectal gel) 5 mg/mL, 10 mg/2 mL, 15 mg/3 mL, and 20 mg/4 mL fixed-dose products from the market for reasons of safety or effectiveness. Such a petition must accompany an abbreviated new drug application ("ANDA") that seeks to rely on a withdrawn drug as the reference listed drug. 21 CFR 314.122(a). Unless FDA finds that the reference product was *not* withdrawn for reasons of safety or effectiveness, the agency must refuse to approve the ANDA. 21 CFR 314.122(c), 314.127(a)(11), and 314.161(a)(1).

As discussed below, FDA required Valeant to quickly and completely withdraw certain configurations of the fixed-dose Diastat® product from the market because the agency had concluded that continued sale of the products posed unacceptable risks to patient safety. The only proper response to the Lachman petition, therefore, is for the agency to determine that those products were withdrawn for reasons of safety. In essence, having concluded that the fixed-dose products had to be removed from the market to avoid confusion (and the medication errors that would result), FDA already has determined that withdrawal of the fixed-dose Diastat® products was for safety reasons.

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Background

Diastat® (diazepam rectal gel) is approved for rectal administration in the management of selected refractory epilepsy patients (age 2 and older) who are on stable regimens of anti-epileptic drugs yet require intermittent use of diazepam to control bouts of increased seizure activity.¹ FDA originally approved Diastat® in July 1997, in five fixed dose syringes: 2.5 mg/0.5 mL, 5 mg/mL, 10 mg/3 mL, 15 mg/3 mL, and 20 mg/4 mL.

On September 19, 2005, FDA approved Diastat® AcuDial™ (diazepam rectal gel), a new delivery system that requires fewer fixed-dose syringes and allows for greater flexibility in dosing. Diastat® AcuDial™ is sold in two syringe sizes; each syringe is designed to provide one of several different doses. Specifically, there is a 10 mg syringe (with a 4.4 cm tip) that can deliver doses of 5 mg, 7.5 mg, and 10 mg, and a 20 mg syringe (with a 6.0 cm tip) that can deliver doses of 10 mg, 12.5 mg, 15 mg, 17.5 mg, and 20 mg.² Each syringe has a locking mechanism and, before dispensing Diastat® AcuDial™, a pharmacist “dials” to the prescribed dose and locks it into place, thus controlling the amount of drug that is administered.

Diastat® AcuDial™ is a portable rescue medicine for breakthrough epileptic seizures. It is specifically approved for administration by a caregiver who is not a healthcare professional, and typically is administered by the parent of a child with epilepsy. Patients and caregivers are educated about the product's safe and effective use by the prescriber and the pharmacist, as part of a rigorous Risk Management Program (“RMP”) that was a condition of approval.

The RMP includes extensive education and training of pharmacists, prescribers, caregivers and patients, as well as enhanced safety monitoring. Among its components:

- Valeant sent two mailings to each of the approximately 60,000 retail pharmacies in the United States.
- Valeant sent educational materials to more than 15,000 doctors who prescribed Diastat® in the previous year.

¹ The active ingredient, diazepam, is controlled as a Schedule IV depressant under the Controlled Substances Act. 21 CFR 1308.14(c)(14).

² Consistent with a post-marketing commitment made to FDA, Valeant is revising the configuration of the 20 mg syringe so that the minimum achievable dose is 12.5 mg.

- Valeant's neurology sales force received specialized training, and in turn provided in-person education and training to almost 15,000 pharmacies that dispense Diastat® and to the doctors (and their nurses) that account for 80% of prescriptions.
- Educational materials for patients and caregivers, including print, website, and video materials, were developed and made widely available.
- Valeant augmented its pharmacovigilance program with additional training for personnel receiving adverse event reports and product complaints, and enhanced reporting obligations, both internally and to FDA.

Withdrawal of Diastat® to Avoid Patient Risk

One important part of the RMP addressed a safety issue that could not be ameliorated by education, training, or pharmacovigilance. FDA recognized the confusion and medication error that likely would result from having the fixed-dose products and Diastat® AcuDial™ on the market at the same time. For example, a caregiver instructed in the use of Diastat® AcuDial™ but dispensed a fixed dose product would, when treating a child experiencing a seizure, find an unfamiliar product for which he or she was not trained. The same would be true if a caregiver who expected to be using a fixed-dose syringe were dispensed a Diastat® AcuDial™. In either case, the situation could easily lead to delayed or improper administration, which would subject the child to serious risks.

Because of these safety issues, FDA required the RMP to include removing from the market the fixed-dose products that would have duplicated doses available with Diastat® AcuDial™.³ Moreover, FDA strongly urged Valeant to act quickly to withdraw the fixed-dose products from sale. Valeant had initially proposed to phase out the fixed-dose products over a six-month period after introduction of Diastat® AcuDial™. FDA, however, wanted the "duration of overlap [to] be as short as possible," if not completely eliminated. March 2, 2005 Letter from Russell Katz, M.D., to Xcel Pharmaceuticals, at 2.⁴ In response to the agency's

³ Valeant continues to market the 2.5 mg fixed dose of Diastat® (which is not a dose available with Diastat® AcuDial™) for use as a partial replacement dose for patients who expel a portion of the prescribed dose. See Diastat® AcuDial™ approved labeling at 3 (under "Dosage and Administration").

⁴ Valeant acquired Xcel Pharmaceuticals in February 2005.

position, the RMP was revised to reduce the market overlap from six months to no more than one or two *days*.

Valeant began to reduce its wholesalers' inventory of Diastat® five weeks before the Diastat® AcuDial™ launch. During this inventory reduction period, Valeant cancelled any orders for the products being discontinued. As the launch date neared, Valeant solicited the return and exchange of any remaining pharmacy stocks of the fixed-dose products. Valeant then shipped Diastat® AcuDial™ to wholesalers by next day air, so that supply would be uninterrupted. Valeant also quickly moved to make obsolete the NDC numbers in the company's internal ordering and distribution systems, to further assure that the fixed-dose products would not be available. All of this was done to avoid the risks to patients that – as the agency clearly recognized – would arise from the fixed-dose products' continued presence on the market.

All of these steps were undertaken in accordance with the RMP, FDA acceptance of which was central to the agency's approval of Diastat® AcuDial™.⁵

Answering the Lachman Petition

The question raised by the Lachman petition is whether the 5 mg/mL, 10 mg/2 mL, 15 mg/3 mL, and 20 mg/4 mL fixed-dose Diastat® products were withdrawn from sale because of safety or effectiveness reasons. In this regard, the record is unequivocal. Patient safety issues are *precisely* what led Valeant to move quickly and comprehensively – at the agency's insistence – to withdraw these products from the market. In essence, FDA has already answered the question posed by the petition. Moreover, a decision to the contrary would open the door to approval of a generic version of the withdrawn products, which would expose patients to the very risks that FDA and Valeant sought to prevent by withdrawing the fixed-dose products.

Accordingly, FDA should find that the fixed-dose Diastat® products were withdrawn for safety reasons, which would require the agency to remove the withdrawn products from listing in *Approved Drug Products with Therapeutic Equivalence Determinations* (the "Orange Book");⁶ publish a notice of the removal in

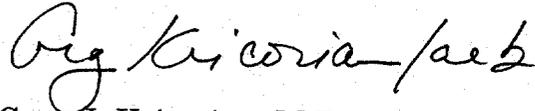
⁵ The approvable letter required submission of additional details regarding "critical aspects" of the RMP, specifically including removal of the fixed-dose products from the market. March 2, 2005 Letter at 1.

⁶ At present, the withdrawn Diastat® products are listed in the Orange Book as "discontinued." A drug product determined to have been withdrawn for safety or

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the Federal Register; and would preclude approval of an ANDA that references any of the withdrawn products.

Respectfully submitted,

A handwritten signature in black ink that reads "Greg Kricorian / aeb". The signature is written in a cursive style with a horizontal line through the middle.

Greg J. Kricorian, M.D.
Director, Medical Affairs

cc: Russell Katz, M.D.

effectiveness reasons must be removed from the Orange Book. 21 CFR 314.3(b), 314.161(e), and 314.162(a)(2).