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

CITIZEN PETITION

Valeant Pharmaceuticals International (Valeant) submits this petition pursuant to section 505 of the Food, Drug, and Cosmetic Act (FDCA), 21 CFR 10.25(a), and 21 CFR 10.30, to request that the Commissioner of Food and Drugs (the Commissioner) take the actions described below with regard to any abbreviated new drug application (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 reference listed drug.

Valeant withdrew those fixed-dose Diastat® products from the market in September 2005, with the launch of Valeant's Diastat® AcuDial™ (diazepam rectal gel), a new delivery system. The withdrawal was done at the Food and Drug Administration's (FDA's) urging, to avoid the risk of confusion and medication error that would result from having Diastat® and Diastat® AcuDial™ products in the same doses available on the market. Pending before the agency is a citizen petition asking FDA to determine whether the discontinued products were withdrawn for reasons of safety or effectiveness.[1] As discussed in Valeant's comments to that petition, because the company withdrew the overlapping doses of Diastat® from the market because of safety concerns, none of the fixed-dose products can serve as the reference listed drug for an ANDA.[2]

This petition addresses related issues that would arise if, in response to the Lachman Petition, the agency were to conclude that the withdrawn products may be the reference product for an ANDA. As discussed below, allowing fixed-dose diazepam rectal gel products onto the market would expose patients to the same risks that led to withdrawal of those

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[1] Citizen Petition submitted by Lachman Consultant Services, Docket No. 2006P-0209/CP1 (May 15, 2006) (Lachman Petition). Such a petition must accompany an ANDA that seeks to rely on a withdrawn product as the reference listed drug. 21 CFR 314.122(a). Unless FDA finds that the reference product was *not* withdrawn for reasons of safety or effectiveness, the agency must refuse to approve the ANDA. 21 CFR 314.122(c), 314.127(a)(11), and 314.161(a)(1).

[2] Valeant Comments, Docket No. 2006P-0209/C2 (Aug. 7, 2006).

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Diastat® products in the first instance. Accordingly, even if a withdrawn product may be the reference product for an ANDA, no such ANDA can be approved.

A. ACTION REQUESTED

Valeant respectfully requests that the Commissioner refrain from approving any ANDA for a diazepam rectal gel that relies on Diastat® 5 mg/mL, 10 mg/2 mL, 15 mg/3 mL, or 20 mg/4 mL as the reference listed drug. If the agency is to permit any reference to these withdrawn products (which, for the reasons stated in Valeant's response to the Lachman Petition, Valeant believes the agency cannot and should not do), it should require the applicant to submit a new drug application (NDA) in accordance with section 505(b)(2) of the FDCA, 21 USC 355(b)(2), because of significant changes in labeling that would be necessary for the safe use of the new product.

B. STATEMENT OF GROUNDS

1. Diastat® AcuDial™

Diastat® 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.[3] FDA approved Diastat® in 1997 in five fixed-dose syringes: 2.5 mg/0.5 mL, 5 mg/mL, 10 mg/2 mL, 15 mg/3 mL, and 20 mg/4 mL.

In September 2005, FDA approved Diastat® AcuDial™, which provides the drug via a new delivery system. It is sold in two syringe sizes, each of which is designed to provide one of several different doses. The 10 mg syringe (which has a 4.4 cm tip) can deliver doses of 5 mg, 7.5 mg, and 10 mg, and the 20 mg syringe (with a 6.0 cm tip) can deliver doses of 10 mg, 12.5 mg, 15 mg, 17.5 mg, and 20 mg.[4] 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.

In preparation for the launch of Diastat® AcuDial™, Valeant removed the Diastat® fixed-dose products from the market.[5] This withdrawal was done quickly, comprehensively, and at FDA's urging, to prevent any meaningful overlap in the products'

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[3] The active ingredient, diazepam, is a Schedule IV depressant under the Controlled Substances Act. 21 CFR 1308.14(c)(14).

[4] Consistent with a post-marketing commitment, Valeant is revising the configuration of the 20 mg syringe so that the minimum deliverable dose is 12.5 mg.

[5] The 2.5 mg/mL syringe, which is not used as an individual dose but is intended only as a partial replacement dose for patients who expel a portion of the prescribed dose, remains on the market. It does not duplicate a dose available with Diastat® AcuDial™.

availability, because, as the agency recognized, differences between the seemingly similar products would likely lead to confusion and medication errors that would put patients at risk.[6]

2. Providing for Safe and Effective Use

The risk of confusion is particularly critical because of how Diastat® AcuDial™ is used. It is a portable rescue medicine for breakthrough epileptic seizures that is specifically approved for administration by a caregiver who is not a healthcare professional. In most instances, the drug is administered by the parent of a child with epilepsy. Accordingly, as a condition of approving Diastat® AcuDial™, FDA required Valeant to implement a risk management program (RMP) that, in addition to withdrawal of the fixed-dose products, includes extensive education and training of pharmacists, prescribers, caregivers, and patients, to ensure safe and effective use of Diastat® AcuDial™, and enhanced safety monitoring to allow evaluation of the RMP's effectiveness.[7]

The RMP reflected the importance of proper administration of the drug, the differences between the fixed-dose syringe and Diastat® AcuDial™, and the features of the new delivery system. Valeant provided direct training for thousands of pharmacists, doctors, and nurses, sent multiple mailings to tens of thousands of retail pharmacies and doctors, and widely disseminated educational materials for patients and caregivers. Valeant also implemented changes to the product's labeling necessitated by the innovative delivery system. For example, pharmacists are now given detailed instructions on how to set the dose to be delivered, and caregivers are directed how to check the dose both when the pharmacist dispenses the product and before using it. The labeling also includes detailed instructions for the safe disposal of any diazepam gel remaining in the syringe after administration.[8]

The RMP also reflected FDA and Valeant's shared view that the presence on the market of both Diastat® AcuDial™ and fixed-dose products with duplicative doses would create a risk of confusion and medication error that could not be adequately mitigated by education and training. 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. This could cause a delay in administering the drug, which would prolong the child's seizure, or improper administration. Also, the caregiver could become concerned about possible over-dosage if, after using a fixed-dose product, he or she did not find any drug remaining in the syringe after use, as would be expected with some doses of Diastat® AcuDial™.

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[6] *See* March 2, 2005 Letter from Russell Katz, M.D., to Xcel Pharmaceuticals, at 2. Valeant acquired Xcel Pharmaceuticals in February 2005.

[7] See Valeant Comments at 2-3.

[8] For example, if the prescribed dose of Diastat® AcuDial™ were 15 mg, 5 mg of drug would remain in the syringe after use.

Similarly, the pharmacist has a crucial responsibility in dialing and locking in the amount of drug to be administered with Diastat® AcuDial™, but the fixed-dose products would require no such intervention. If pharmacists must be familiar with both products, there is an enhanced risk that a pharmacist may forget to lock in the proper dose before dispensing Diastat® AcuDial™, or may do so incorrectly. An error that results in an over-dosage of this controlled substance can dangerously depress respiration, among other things; an ineffective dose may allow the patient's seizure to continue.

These risks are real and unavoidable if both Diastat® AcuDial™ and fixed-dose products are on the market. That is why FDA and Valeant agreed that the fixed-dose products had to be withdrawn from the market, quickly and completely. Valeant began the process five weeks before the Diastat® AcuDial™ launch, with the goal of reducing the market overlap of the products to no more than one or two days.

3. A Fixed-Dose Diazepam Rectal Gel Cannot be Safely Marketed with the Withdrawn Diastat® Product Labeling.

If FDA were to approve an ANDA for a fixed-dose diazepam rectal gel that referenced a withdrawn Diastat® product, it would create the market situation – and attendant patient risks – that led Valeant to withdraw the fixed-dose products. If a fixed-dose product were to come onto the market, therefore, the risks of confusion and medication error would have to be addressed in the product's labeling, as well by educating and training doctors, pharmacists, caregivers, and patients. This would require extensive changes from the labeling for the withdrawn Diastat® products that go well beyond the labeling differences that are permitted in the context of an ANDA. Accordingly, a sponsor seeking to rely on a withdrawn Diastat® product to obtain approval of a fixed-dose diazepam rectal gel product must do so by means of an NDA in accordance with FDCA section 505(b)(2).

As a general rule, the labeling for a generic drug must be the same as the labeling for the reference listed drug. 21 USC 355(j)(2)(A)(v). The FDCA provides only two exceptions to this requirement: changes to the labeling based on product differences pursuant to a suitability petition, and labeling differences required because the products are produced or distributed by different manufacturers. *Id.* The second exception has been defined by regulation to permit differences in expiration date, formulation, bioavailability, or pharmacokinetics; revisions made to comply with current FDA labeling guidelines or other guidance; and the omission of an indication or other aspect of labeling protected by patent or accorded exclusivity. 21 CFR 314.94(a)(8)(iv), 314.127(a)(7). Except for the permitted differences, therefore, a generic fixed-dose diazepam rectal gel product that relies on a withdrawn Diastat® product as the reference listed drug must have labeling that is the same as what was approved for the withdrawn product at the time it was discontinued.

None of the exceptions would allow for the labeling that would be necessary to safely market a generic fixed-dose product. FDA has determined that having fixed-dose products on the market at the same time as Diastat® AcuDial™ creates a significant risk of

medication error. The labeling of the Diastat® fixed-dose products contains no warnings or other information to address that risk, of course, because those products were withdrawn from the market in advance of Diastat® AcuDial™. Similarly, Valeant's RMP, which includes a substantial and continuing education and training program, was adopted with marketing of Diastat® AcuDial™, and not the withdrawn products. But a generic fixed-dose product could not be safely marketed concurrent with Diastat® AcuDial™ unless the fixed-dose product's labeling addressed the risks of confusion, and unless healthcare professionals, caregivers, and patients were educated and trained to avoid medication errors. The labeling would also have to reflect the fact that, at this point, most targeted doctors, nurses, pharmacists, caregivers, and patients have been trained in proper prescribing, dispensing, and use of Diastat® AcuDial™ -- all of which differs from Diastat®. But neither the statute nor regulations permit changes of that scope and nature to the labeling for the withdrawn products. As FDA has said:

> [T]he exceptions to the requirement that a generic drug's labeling be the same as that of the listed drug are limited. The agency will not accept ANDA's for products with significant changes in labeling (such as new warnings or precautions) intended to address newly introduced safety or effectiveness problems not presented by the listed drug. Such labeling changes do not fall within the limited exceptions in [the statute].

ANDA Proposed Rule, 54 Fed. Reg. 28872, 28884 (July 10, 1989).[9]

To be safely marketed, a generic fixed-dose diazepam rectal gel product would require labeling that differs significantly from that approved for the withdrawn Diastat® products. It would also require a risk minimization action plan (RiskMAP), most likely with a scope and components similar to the Diastat® AcuDial™ RMP, because it would need to reach the same audiences and gather information on the same safety issues.[10] In addition, however, the RiskMAP also would have to address the unique risks of product confusion and medication error that would be created by the generic sponsor's marketing of a fixed-dose product that duplicates a strength in which Diastat® AcuDial™ is available. The necessary labeling and RiskMAP fall well outside the labeling differences permitted in an ANDA, however, and therefore preclude approval of an ANDA referencing the withdrawn Diastat® products.

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[9] *Cf. Zeneca, Inc. v. Shalala*, 213 F.3d 161, 169 (4th Cir. 2000) (permitting the addition of a sulfite warning to the labeling of a generic drug, but only where that warning was required by a difference in formulation and a specific FDA regulation).

[10] "Risk minimization action plan/RiskMAP" has replaced "risk management program/RMP" as the term used to described these undertakings. *Compare* Concept Paper: Risk Management Programs (Mar. 3, 2003) *with* Guidance for Industry: Development and Use of Risk Minimization Action Plans (Mar. 2005).

5. Conclusion

Diazepam rectal gel is a controlled substance depressant indicated for use in epileptic children. The risks of medication error with such a drug in such a population must be taken seriously. FDA has recognized the significant and unavoidable risks of confusion and medication error that would result from having on the market fixed-dose diazepam rectal gel products that duplicate dosage strengths available with Diastat® AcuDial™. Valeant addressed those risks by withdrawing its duplicative fixed-dose products from the market. If a generic fixed-dose product were now to enter the market, its safe marketing would require labeling that would differ meaningfully from the labeling approved for the reference listed drug. Because the necessary labeling and RiskMAP would differ from the Diastat® labeling in ways not permitted for an ANDA, the Commissioner should not approve an ANDA for a fixed-dose diazepam rectal gel that seeks to rely on a withdrawn Diastat® product as the reference listed drug.

C. ENVIRONMENTAL IMPACT

This petition is categorically exempt from the requirement for an environmental assessment or environmental impact statement pursuant to 21 CFR 25.30 and 25.31.

D. ECONOMIC IMPACT

Information on the economic impact of the petition will be provided on request.

E. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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cc: Docket 2006P-0209