



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-648/S-008

Xcel Pharmaceuticals, Inc.
Attention: Bruce J.C. Lu, R.Ph., RAC
Director, Regulatory Affairs
6363 Greenwich Drive, Suite 100
San Diego, CA 92122

Dear Mr. Lu:

Please refer to your supplemental new drug application dated November 4, 2004, received November 5, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diastat AcuDial (diazepam rectal gel) Rectal Delivery System Pediatric 10mg and Adult 20mg

We acknowledge receipt of your additional submissions dated November 15, 2004, November 29, 2004, December 14, 2004, and February 16, 2005.

This supplemental new drug application provides for a second generation drug delivery system for Diastat (diazepam rectal gel) Rectal Delivery System. Specifically, this new system consists of pre-filled unit-dose syringes (two configurations) that can deliver varying quantities of diazepam 5 mg/mL: a 10 mg syringe with a 4.4 cm tip (that can deliver doses of 5, 7.5, and 10 mg) and a 20 mg syringe with a 6.0 cm tip (that can deliver doses of 10, 12.5, 15, 17.5, and 20mg).

We have completed our review of this application, as amended, and have concluded that it is approvable. Before the application may be approved, you will need to address the following issues.

As you know, we have been concerned about the possibility that, in the context of a busy pharmacy setting, pharmacists may not accurately dial and lock-in the appropriate dose in the syringe. We recognize that you are confident that pharmacists will reliably accomplish this task, based on the results of your field test. However, in our view, that test did not adequately test this question (we acknowledge that you have demonstrated that pharmacists can reliably dial and lock-in the correct dose; that is, that they can understand and follow the instructions). Because we are still concerned about the possibility that pharmacists may dispense syringes with the incorrect dose, we have the following comments:

Risk Management Program (RMP)

Although you have included a description of your RMP, we would like to see additional details for some of the critical aspects.

In particular, please submit the details of how you will contact the various relevant groups (pharmacists, physicians, nurses, patients) to educate them about the new syringes. We are particularly

interested in the details of how you will educate these constituencies (e.g., specific details of your plans to contact these groups, and specific documents you will use in these efforts).

We note that you plan for your educational plan to be "continuous", but you have provided no details. Please provide the details of your plans to enact the RMP on a continuous basis. We would also like you to provide the specific details of your plans to contact and inform patients about how to check the syringe to confirm the dose. In this regard, although you conclude that caregivers can adequately perform this function, your data suggest otherwise. % of caregivers were able to "correctly perform the compliance check", and the lower and upper limits on the percent of detectable errors was % and % respectively; we do not believe that these results suggest that patients can do this reliably).

We also note that you state that a pre-printed prescription pad will "clarify" for the prescriber and pharmacist the difference between the maximum dose and the prescribed dose to be dialed and locked in. Please provide a sample of these pads, and describe how this pad will provide this clarification.

You also suggest that your "existing pharmacovigilance program" will assess the success of your plan; please provide a detailed description of how this will be achieved.

We recognize that, under your current plan, the new and old syringes will be in the marketplace at the same time for between three and six months. We recommend that this duration of overlap be as short as possible, and would like to discuss with you the possibility that this can be avoided. If the products are to be available at the same time (regardless of the duration), we believe that you will need to be aggressive about informing the relevant parties about this co-existence, to avoid confusion. We would like to see the details of this portion of the plan.

Packaging and Labeling

We recommend that you make several changes to the product package.

Specifically, we recommend that you include on the primary panel that is directed to pharmacists a statement that the product should not be dispensed until a dose has been dialed and locked in. We also suggest that different colors be used for different messages, in order to make these statements more noticeable. Some effort should also be expended to explicitly remind the pharmacist that the dose must be dialed and locked in for both syringes in the pack.

Currently, you have proposed the same color (red) for the description of both the 10 and 20 mg syringes. We recommend that you develop a separate major color scheme for each strength. We also recommend that you describe all possible doses that each syringe can provide, not just the maximum dose, prominently on the package and in the package insert.

We recommend that you consider abandoning the designation of "pediatric" and "adult" for the 10 and 20 mg syringes, respectively. Current labeling recommends doses greater than 10 mg for a substantial number of pediatric patients, and the designation of the 20 mg syringe as "adult" when it will be used for a number of pediatric patients may cause confusion among prescribers, pharmacists, and, especially, caregivers.

We recommend that your educational materials make it clear that the prescription label should not be placed on the front panel of the package until the cardboard card has been removed (we are concerned that if the label is placed on the front panel while the card is in place, it could obscure critical

information for the pharmacist). In this regard, the statement on the card telling the pharmacist that the card should be discarded after use should be more prominently displayed than it is in the current proposal. In addition, a warning to pharmacists to not place the prescription label on the syringe in such a way as to obscure the dose window (some states require that the prescription label be placed directly on the syringe) should be included in appropriate educational materials.

Regarding labeling, we recommend that you change the caregiver administration and disposal instruction sheet to include appropriate pictures next to the section that informs caregivers to confirm the dose and that the green "ready" band is visible. Alternatively, although less desirable, the patient should be referred to the display sheet on the bottom of the package. Indeed, at this time, it is unclear to us how the caregiver would know that such a panel exists and that it is on the bottom of the package. In addition, the picture describing the disposal procedures on the "How to Administer Diastat" sheet is quite small; we suggest that it be enlarged.

Given the results of your caregiver assessment study, some patients/caregivers may not be able to confirm the dose, as your proposed labeling directs them. For this reason, we recommend that, wherever confirmation of the dose is directed, the phrase "...if possible" be added.

Finally, please address the following miscellaneous comments:

- Please omit all terminal zeros in the description of doses (e.g., write 20 mg, not 20.0 mg) in all printed materials.
- Remove the disposal instructions at the bottom of the caregiver "Administration and Disposal Instructions" sheet. These are misplaced in this location. On the "How To Administer" sheet, we recommend that you change Box 14 to a Box 14a, entitled Disposal Instructions for AcuDial. These instructions should incorporate both the text at the bottom of the "Administration and Disposal Instructions" sheet and the picture in the currently proposed Box 14. Then add a Box 14b, entitled Disposal Instructions for 2.5mg Diastat consisting of the text currently at the bottom of the "Administration and Disposal Instructions" sheet.
- Reconcile the storage conditions listed on the package insert with those on the devices and device containers. They should match exactly.
- The course of action to be taken by the pharmacist who inadvertently locks the collar prior to dose dialing should be clearly stated in labeling and be included as part of the RMP.

Post-Marketing Issues

We believe that the dose window and size of the print used for the dose are too small. We would like to discuss with you enlarging both post-marketing. Also, you should consider making 12.5 mg, not 10 mg, the minimum dose achievable with the 20 mg syringe. A dose of 10 mg can, obviously, be achieved with the 10 mg syringe, and including the 10 mg dose in the 20 mg syringe has the potential to cause confusion (i.e., which syringe should be dispensed if a dose of 10 mg is prescribed), and add unnecessary risk (with a 10 mg minimum dose in the 20 mg syringe, the maximum overdose, in the case where the pharmacist does not dial or lock in the dose would be 10 mg, whereas if the 10 mg dose was only available in the 10 mg syringe, such an error could not occur).

Proprietary Name

Your proposed propriety name of Diastat AcuDial for this new delivery system has been found to be acceptable. This decision, however, is considered to be tentative, and the propriety name will need to be re-evaluated approximately 90 days prior to the expected final approval of this application.

Promotional Material

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Other

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Jacqueline H. Ware, Pharm.D., Senior Regulatory Project Manager, at (301) 594-5533.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research