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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-549

Approval Letter(s)

HELSINN EXHIBIT 2002
Azurity Pharmaceuticals, Inc. v. Helsinn Healthcare S.A.
IPR2025-00945

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-549

Merck & Company, Inc.
Attention: Steven A. Aurecchia, M.D.
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Aurecchia:

Please refer to your new drug application (NDA) dated September 27, 2002, received September 27, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMEND® (aprepitant) Capsules.

We acknowledge receipt of your submissions dated November 5, November 19, November 25, and December 27, 2002 and January 6, January 7, January 8, January 15, January 16, January 22, February 12, February 14, February 27, March 11, March 14, March 17, March 18, March 19, March 20, March 21, March 24, and March 26, 2003.

This new drug application provides for the use of EMEND® (aprepitant) Capsules in combination with other antiemetic agents, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert) and submitted labeling (immediate container and carton labels submitted February 27, 2003). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-549.**" Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated March 24, 2003. These commitments are listed below.

1. Commitment #1

Merck will obtain pharmacokinetic interaction data on a total of 10 patients receiving concomitant aprepitant and docetaxel (an IV chemotherapy CYP3A4 subtrate), instead of the originally planned 20 patients (Protocol 051, Serial No. 242, IND

The timeline is as follows:

- Completion of patient portion (N = 10) — 4th Quarter 2003
- Submission of Clinical Study Report — 2nd Quarter 2004

2. Commitment #2

Merck will conduct a drug interaction study to evaluate the effect of aprepitant on either vinorelbine or irinotecan.

The timeline is as follows:

- Protocol Submission — 1st Quarter 2004
- Completion of patient portion of study — 4th Quarter 2005
- Submission of Clinical Study Report — 3rd Quarter 2006

3. Commitment #3

Merck will conduct a drug interaction study in healthy subjects, including some who are CYP2D6 poor metabolizers, to evaluate the effect of aprepitant on dolasetron.

The timeline is as follows:

- Draft Clinical Study Protocol to FDA — 4th Quarter 2003
- Completion of patient portion of study — 2nd Quarter 2004
- Submission of Clinical Study Report — 4th Quarter 2004

4. Commitment #4

Merck will initiate a risk management program as outlined in the submission to NDA 21-549 dated March 18, 2003, to ensure that health care providers understand the approved indication for EMEND and precautions with its use and to address and minimize potential for confusion with AMEN or VFEND and EMEND. Merck will submit all medication error reports relating to tradename confusion, both potential and actual, that occur with EMEND for a period of one year following the date of approval. All actual and potential errors will be submitted as 15-day reports regardless of patient outcome. Merck agrees to evaluate these data with FDA and, if needed, to implement intervention to further minimize risk of medication errors.

For the duration of the program, Merck also commits to providing the following: 1) reports on the proactive surveillance audit with retail pharmacists on a quarterly basis beginning no later that the fourth quarter of 2003; 2) an annual summary report beginning in the fourth quarter of 2004.

5. Commitment #5

Merck will submit to FDA a report on the assessment of the inhibitory properties of aprepitant on CYP2C8 and CYP2B6 *in vitro* in human liver microsomes.

The timeline is as follows:

- Submission of final report to FDA 2nd Quarter 2003

6. Commitment #6

Merck commits to justify the use of [redacted] method, including studies on the [redacted] for the nanoparticle formulation. Accordingly, based on the data presented in the response, the dissolution specification will be reviewed and, if warranted, revised.

The timeline is as follows:

- Submission of information to FDA 2nd Quarter 2003

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as

responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

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

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Brian Strongin, R.Ph., M.B.A., Regulatory Project Manager at (301) 827-7473.

Sincerely,

/S/
{See appended electronic signature page}

Florence Houn, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Julie Beitz
3/26/03 09:52:36 AM
Julie Beitz MD signing for Florence Houn MD