DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-576/S-008

Jazz Pharmaceuticals, Inc.
Attention: Jennifer Ekelund
Director, Regulatory Affairs
3180 Porter Drive
Palo Alto, CA 94304

Dear Ms. Ekelund:

Please refer to your supplemental new drug application dated May 31, 2005, received June 1, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cystadane (betaine anhydrous for oral solution).

We acknowledge receipt of your submissions dated November 17, 2005 (SPL) and February 7, 2006 (by email; MS Word).

Although this supplement was submitted as a Changes Being Effected Supplement, you indicated in a February 7, 2005, telephone call with Ms. Enid Galliers that Supplement-008 should have been a prior approval supplement. We have made that administrative change.

This supplemental new drug application provides for the following changes to the package insert.

1. In the fifth paragraph of the CLINICAL PHARMACOLOGY section, the phrase "over baseline" was inserted in the first sentence to read, "In CBS-deficient patients, large increases in methionine levels over baseline have been observed," and the second sentence, "However, the increased methionine levels do not appear to have been associated with adverse clinical consequences," has been deleted from that paragraph.

2. In the PRECAUTIONS section, the following subsection, "Hypermethioninemia," was added.

   Hypermethioninemia

   Patients with homocystinuria due to cystathionine beta-synthase (CBS) deficiency may also have elevated plasma methionine concentrations. Treatment with Cystadane may further increase methionine concentrations due to the remethylation of homocysteine to methionine. Cerebral edema has been reported in patients with hypermethioninemia, including a few patients treated with Cystadane. Plasma methionine concentrations should be monitored in patients with CBS deficiency. Plasma methionine concentrations should be kept below 1,000 umol/L through dietary modification and, if necessary, a reduction of Cystadane dose.

3. In the ADVERSE REACTIONS section, the sentence, "No other types of adverse effects have been reported," was replaced with the following:

   "A few cases of cerebral edema have been reported secondary to severe hypermethioninemia in patients with cystathionine beta-synthase (CBS) deficiency treated with Cystadane. See PRECAUTIONS: Hypermethioninemia."

4. In the first paragraph of the DOSAGE AND ADMINISTRATION section, the titration instruction for pediatric patients less than 3 years of age was changed from "and then increased weekly by 100 mg/kg increments" to "and then increased weekly by 50 mg/kg increments." The revised sentence now reads, "In pediatric patients less than 3 years of age, dosage may be started at 100 mg/kg/day and then increased weekly by 50 mg/kg increments."

5. A new sentence was inserted immediately before the next to last sentence of the first paragraph of the DOSAGE AND ADMINISTRATION section. The inserted sentence is, "In one study by Matthews[i] et al., pharmacokinetic and pharmacodynamic simulation indicated minimal benefit from exceeding a twice-daily dosing schedule and a 150 mg/kg/day dosage for betaine."

6. The reference to Matthews et al. was added as a footnote at the end of the package insert as follows:

   [i] Matthews A, Johnson TN, Rostami-Hodjegan A, Chakrapani A, et al. An indirect response model of homocysteine suppression by betaine: optimizing the dosage regimen of betaine in homocystinuria. Br J Clin Pharmacol 2002; 54:140-146.

7. In the first paragraph of the DOSAGE AND ADMINISTRATION section, the word "total" was inserted between "plasma" and "homocysteine" so the sentence reads, "Dosage in all patients can be gradually increased until plasma total homocysteine is undetectable or present only in small amounts."

8. The following two sentences were added to end of the first paragraph in the DOSAGE AND ADMINISTRATION section.

   "Plasma methionine concentrations should be monitored in patients with CBS-deficiency. See PRECAUTIONS: Hypermethioninemia."

We completed our review of this application, as amended. This application 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).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs*. 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 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 20-576/S-008**." Approval of this submission by FDA is not required before the labeling is used.

Due to a reorganization of assignments among new drug review divisions, responsibility for this application has been transferred to the Division of Gastroenterology Products. Contact information for the project manager appears below. Your submission of FPL for this supplement and all other future submissions to this NDA should be addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Attention: Division of Gastroenterology Products
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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 regarding this supplement, call Enid Galliers, Chief, Project Management Staff, Division of Metabolism and Endocrinology Products, at (301) 796-1211.

If you have any other questions about this application, call Ryan Barraco, Regulatory Project Manager, Division of Gastroenterology Products, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Acting Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
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/

Mary Parks

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