DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-676/S-022

B.Braun Medical Inc.
2525 McGaw Avenue
P.O.Box 19791
Irvine, CA 92623-9791

Attention: Pushpa Mehta, RAC
Regulatory Affairs Specialist

Dear Ms. Mehta:

Please refer to your supplemental new drug application dated December 29, 2003, received December 31, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for HepatAmine (amino acid injections).

This supplemental new drug application provides for revised **PRECAUTIONS** and **WARNINGS** sections of the package insert, and revised release specification and stability protocol containing a test for aluminum determination with a validated analytical method and an acceptance criterion of NMT 25 mcg/L of aluminum in accordance with the requirements of 21 CFR 201.323.

The following revisions are made to the package insert.

1. The following changes are made to the **WARNINGS** section.

   a. The second sentence of the third paragraph is revised to read:

      Frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of parenteral nutrition**.**

   b. As per the requirements of 21 CFR 201.323 the following information is added.

      This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphorous solutions, which contain aluminum.

      Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5mcg/kg/day accumulate aluminum at levels associated with central nervous

system and bone toxicity. Tissue loading may occur at even lower rates of administration.

2. The following changes are made to the **PRECAUTIONS** section.

a. As per the requirements of 21 CFR 201.323, the following statement is added.

Drug product contains no more than 25 mcg/L of aluminum.

b. The following information is added under the title **"Laboratory Tests."**

Frequent clinical evaluation and laboratory determinations are necessary for proper monitoring during administration.

Laboratory tests should include measurement of blood sugar, electrolyte, and serum protein concentration, kidney and liver function tests, and evaluation of acid-base balance and fluid balance. Other laboratory tests may be suggested by the patient's condition.

c. The following information is added under the heading "**Drug Interactions.**"

Some additive**s** may be incompatible. Consult with pharmacist. When introducing additives, use aseptic techniques. Mix thoroughly. Do not store.

d. The subsection **"Carcinogenesis, Mutagenesis, Impairment of fertility**" is added as follows.

No in vitro or in vivo carcinogenesis, mutagenesis, or fertility studies have been conducted with HepatAmine (8% Amino Acid Injection).

e. The subsection title "**Usage in Pregnancy**" is changed to "**Pregnancy-Teratogenic Effects.**"

f. The subsection **"Labor and Delivery"** is added as follows.

Information is unknown.

g. The subsection **"Nursing Mothers**" is added as follows.

It is not know whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HepatAmine is administered to a nursing woman.

h. The subsection **"Pediatric Use**" is added as follows.

Safety and effectiveness of amino acid injections in pediatric patients have not been established by adequate and well-controlled studies. However, the use of amino acid injections in pediatric patients as an adjunct in the offsetting of nitrogen loss or in the treatment of negative nitrogen balance is well established in the medical literature. See **WARNINGS** and **DOSAGE AND ADMINISTRATION**.

i. In accordance with the requirements of 21 CFR 201.57(f)(10)(i), a "**Geriatric Use"** subsection is added as follows.

Clinical studies of HepatAmine did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. See **WARNINGS**.

3. The **DOSAGE AND ADMINISTRATION** section is revised as follows..

a. A **"Pediatric Use"** subsection is added as follows.

Use of HepatAmine in pediatric patients is governed by the same considerations that affect the use of any amino acid solution in pediatrics. The amount administered is dosed on the basis of grams of amino acids/kg of body weight/day. Two to three g/kg of body weight for infants with adequate calories are generally sufficient to satisfy protein needs and promote positive nitrogen balance. Solutions administered by peripheral vein should not exceed twice normal serum osmolarity (718 mOsmol/L).

b. The following statement is added at the end of the third paragraph.

In pediatric patients, the final solution should not exceed twice normal serum osmolarity (718 mOsmol/L).

4. The section "**Directions for Use of B.Braun Glass Containers**" is revised . The instructions for "Products with Air Tube" are deleted.

We have completed the review of this application and it is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted December 29, 2003.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). 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. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 18-676/S-022." Approval of this submission by FDA is not required before the labeling is used.

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, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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 Kim Compton, Regulatory Project Manager, at (301) 827-7410.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Bob Rappaport

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