DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-018/S-018

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 November 21, 2003, received November 24, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TrophAmine (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.

Additionally, the following revisions are made to the package insert.

1. The following statement is added to the **INDICATIONS AND USAGE** section.

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

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

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

      Frequent <u>clinical</u> 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.

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

a. The following statement is added at the end of the seventh paragraph.

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

b. 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.

c. 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.

d. 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.

e. The subsection title "**Usage in Pregnancy**" is changed to "Pregnancy**-Teratogenic Effects**". The following statement is added at the end.

TrophAmine should be given to a pregnant woman only if clearly needed.

f. 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 TrophAmine is administered to a nursing woman.

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

As in all cases of fluid and electrolyte replacement and parenteral nutrition, careful monitoring and special caution is required in pediatric use, specially in pediatric patients with renal failure, acute sepsis, or low birth weight.

The total volume of nutritional fluid and the rate of administration in each patient will be based on individually calculated maintenance and/or replacement fluid requirements, and nutritional needs, and will vary with the child's age, body weight, and renal function.

In neonates and very small infants, particularly careful monitoring will be required to maintain fluid and electrolyte balance, including monitoring of blood glucose. See **INDICATIONS AND USAGE, WARNINGS** and **DOSAGE AND ADMINISTRATION** for additional information.

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

TrophAmine has not been studied in geriatric patients. Elderly patients are known to be more prone to fluid overload and electrolyte imbalance than younger patients. This may be related to impairment of renal function which is more frequent in an elderly population. As a result the need for careful monitoring of fluid and electrolyte therapy is greater in the elderly. All patients, including the elderly, require an individual dose of all parenteral nutritional products to be determined by the physician on an individual case-by-case basis, which will be based on the body weight, clinical condition and the results of laboratory monitoring tests. There is no specific geriatric dose. See **WARNINGS.**

6. The following information is added to the **DOSAGE AND ADMINISTRATION/ Peripheral Parenteral Nutrition** section.

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

7. 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 November 21, 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 19-018/S-018." 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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