DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Zak Hassanein, President
PrimaPharm, Inc.
3443 Trip Court, Suite A
San Diego, CA 92121

RE: NDA #21-716
Hydase™ (hyaluronidase Injection, USP) 150 Units/mL
MACMIS ID #14365

WARNING LETTER

Dear Mr. Hassanein:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed two sales aids (LAB-61 Rev Original and LAB-62 Rev Original) for Hydase™ (hyaluronidase injection) by PrimaPharm, Inc. (PrimaPharm) submitted under cover of Form FDA 2253. Both sales aids are misleading in that they present efficacy and safety claims for Hydase, but fail to communicate **any** risks associated with its use. Thus, the sales aids misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §§352(a) and 321(n); cf. 21 C.F.R. 202.1(e)(3)(i). The sales aids raise public health and safety concerns through their complete omission of risk information for Hydase by suggesting Hydase is safer than has been demonstrated.

Background

According to the Indications and Usage section of the FDA-approved product labeling (PI):

> Hydase™ is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents.

The PI also explains that Hydase is associated with several risks. It states (in pertinent part):

> **WARNINGS**
> Discontinue Hydase™ (hyaluronidase injection) if sensitization occurs.
>
> Hyaluronidase should not be used to enhance the absorption and dispersion of dopamine and/or alpha agonist drugs.
>
> Hyaluronidase should not be injected into or around an infected or acutely inflamed area because of the danger of spreading a localized infection.

Hyaluronidase should not be used to reduce the swelling of bites or stings.

Hyaluronidase should not be applied directly to the cornea.

Hyaluronidase should not be used for intravenous injections because the enzyme is rapidly inactivated.

PRECAUTIONS
General
Furosemide, the benzodiazepines and phenytoin have been found to be incompatible with hyaluronidase.

When considering the administration of any other drug with hyaluronidase, it is recommended that appropriate references first be consulted to determine the usual precautions for the use of the other drug; e.g., when epinephrine is injected along with hyaluronidase, the precautions for the use of epinephrine in cardiovascular disease, thyroid disease, diabetes, digital nerve block, ischemia of the fingers and toes, etc., should be observed.

ADVERSE REACTIONS
The most frequently reported adverse experiences have been local injection site reactions. Hyaluronidase has been reported to enhance the adverse events associated with co-administered drug products. Edema has been reported most frequently in association with hypodermoclysis. Allergic reactions (uticaria, angioedema) have been reported in less than 0.1% of patients receiving hyaluronidase. Anaphylactic-like reactions following retrobulbar block or intravenous injections have occurred, rarely.

Omission of Important Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The sales aids present numerous efficacy and safety claims for Hydase, but fail to communicate **any** risk information. For example, the sales aids make various efficacy claims for Hydase, including:

- "Good news spreads fast: Hyaluronidase is back"
- "New preservative-free formulation"
- "Clinically tested for allergenicity"
- "Highly purified hyaluronidase extract"
- "Hyaluronidase is available again as a spreading agent"
- "Hyaluronidase is available again for use as a spreading agent for injectable anesthesia in ophthalmic surgery."

The sales aids entirely omit risk information, including the most frequently reported adverse experiences, precautions, and warnings from the PI. We note that the PI is printed on the back of the sales aids, but this is not sufficient to provide appropriate qualification or pertinent information for

claims made in the sales aids. For the pieces to be non-misleading, they must contain risk information in each part as necessary to qualify any safety or effectiveness claims made in that part.

Conclusion and Requested Action

For the reasons discussed above, the sales aids misbrand Hydase in violation of the Act. 21 U.S.C. §§352(a) and 321(n); cf. 21 C.F.R. 202.1(e)(3)(i).

DDMAC requests that PrimaPharm immediately cease the dissemination of violative promotional materials for Hydase such as those described above. Please submit a written response to this letter on or before July 14, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for Hydase, such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705, facsimile at (301) 796-9877. In all future correspondence regarding this matter, please refer to MACMIS ID #14365 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Hydase comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Thomas Abrams

6/29/2006 03:40:02 PM