DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

**TRANSMITTED BY FACSIMILE**

Paul D. Krause, PhD
Director, Regulatory Affairs
ISTA Pharmaceuticals, Inc
15295 Alton Parkway
Irvine, CA 92618

**RE: NDA # 21-640**
**Vitrase (hyaluronidase injection) Ovine, 200 USP Units/mL**
**Vitrase (hyaluronidase injection) Lyophilized, Ovine 6200 USP Units**
**MACMIS ID # 13441**

Dear Dr. Krause:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a journal advertisement (ad) (VIT301-09/04) for Vitrase (hyaluronidase injection) submitted by ISTA Pharmaceuticals, Inc. (ISTA) under cover of Form FDA 2253. The journal ad is false or misleading because it fails to reveal material facts, thus minimizing the risks associated with treatment with Vitrase in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(n), 321(n), and FDA implementing regulations, 21 CFR 202.1(e)(3)(i), (5)(i), (iii).

**Background**

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

> Vitrase (hyaluronidase injection) 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.

Furthermore, according to the PI, Vitrase is associated with several risks, including the following Warnings:

> Discontinue Vitrase (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.

The PI includes the following Precautions:

> 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….

**Omission of Important Risk Information**

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. The journal ad fails to present the most serious and frequently occurring risks associated with the use of Vitrase. Although the journal ad presents several effectiveness claims for Vitrase, it fails to include **any** of the warnings associated with use of the drug or the precaution regarding the incompatibility with furosemide, benzodiazepines, and phenytoin as stated above. The only risk information included in the ad is excerpted from the Adverse Reactions section of the PI. By omitting the most serious and frequently occurring risks associated with the drug, the journal ad misleadingly suggests that Vitrase is safer than has been demonstrated.

**Conclusion and Requested Action**

For the reasons discussed above, the journal ad fails to reveal material facts, thus minimizing important risks associated with Vitrase treatment. Accordingly, the journal ad misbrands Vitrase in violation of the Act and FDA implementing regulations. See 21 U.S.C. §§ 352(n), 321(n); 21 CFR 202.1(e)(3)(i), (5)(i), (iii).

DDMAC requests that ISTA immediately cease the dissemination of violative promotional materials for Vitrase such as those described above. Please submit a written response to this letter on or before November 16, 2005, stating whether you intend to comply with this request, listing all violative promotional materials for Vitrase such as those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266 or facsimile at 301-796-9878. In all future correspondence regarding this matter, please refer to MACMIS ID # 13441 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 Vitrase comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

*{See appended electronic signature page}*

Suzanne Berkman, PharmD
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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

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/s/

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Suzanne Berkman

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