



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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Kent S. Allenby, MD, FACP
Vice President, Clinical Research &
Medical Affairs
Baxter Healthcare Corporation;
Anesthesia & Critical Care
95 Spring Street
New Providence, New Jersey 07974

Re: Docket No. 2003P-0494/CP1

Dear Dr. Allenby:

This letter responds to your citizen petition dated October 24, 2003 (Petition), filed on behalf of Baxter Healthcare Corporation (Baxter). Baxter is currently the holder of new drug application (NDA) 06-343 for hyaluronidase for injection and hyaluronidase injection (Wydase). Marketing under this application was discontinued in 2000 by Wyeth, the previous holder of this NDA. Wydase is indicated for use 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. Baxter acquired the NDA for Wydase in January 2003. With the exception of this petition, Baxter has not notified the Agency of any plans to market hyaluronidase. Because Baxter is not currently manufacturing Wydase, there is a shortage of this medically useful product.

You ask that the Food and Drug Administration (FDA) refuse to approve any NDA for a hyaluronidase product unless the conditions set forth in your petition are satisfied. Specifically, you ask that the safety and effectiveness of any new hyaluronidase product:

- Be proven by adequately designed and powered clinical trials, or
- Be shown to be equivalent to Wydase, or
- Be ensured by utilizing an identical raw material source and a comparable production process, resulting in a finished product that can be adequately characterized and shown fully equivalent to Wydase.

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FDA has considered information submitted in your petition, as well as comments submitted to the docket dated February 6, 2004, and other information. We address your requests in this response. For the reasons explained below, your petition is denied.

I. Background

The hyaluronidases are a family of β , 1-4 endoglucosaminidases that depolymerize hyaluronic acid (HA) and chondroitin sulfate. In simpler terms, hyaluronidases are enzymes that break down hyaluronic acid and chondroitin sulfate. This function is well-understood and described in the literature.

Hyaluronidase used in approved drug products is derived from partially purified preparations sourced from mammalian testicular tissue. Although these naturally occurring hyaluronidases have never been fully characterized with respect to chemical structure and impurities, the activity of these enzymes in breaking down hyaluronic acid can be effectively measured by a standard *United States Pharmacopeia* (USP) assay.¹

Hyaluronidase products have been legally marketed in the United States for more than 50 years. In 1948, FDA permitted Wyeth to market Wydase based on a review of literature demonstrating its safety. Subsequently, FDA allowed other hyaluronidase drug products to be marketed based on a safety review, including Alidase in 1949 and Hyazyme in 1951.

In 1962, Congress amended the Federal Food, Drug, and Cosmetic Act (the Act) to require that a new drug be shown to be effective, as well as safe, to obtain FDA approval. This amendment required FDA to conduct a retrospective evaluation of the effectiveness of the drug products that FDA had permitted on the market as safe through the new drug review process between 1938 and 1962. FDA contracted with the National Academy of Sciences/National Research Council (NAS/NRC), Drug Efficacy Study Group, to make an initial evaluation of the effectiveness of over 3,400 products that had been evaluated only for safety between 1938 and 1962.

The efficacy of hyaluronidase for injection, USP, and hyaluronidase injection, USP, was established through FDA's evaluation of the Drug Efficacy Study Implementation (DESI) reports for hyaluronidase (DESI 6343) prepared by the NAS/NRC. The Agency's conclusions regarding the DESI reports for hyaluronidase were published in the *Federal Register* on September 23, 1970 (35 FR 14800-1).

The DESI findings established the clinical effectiveness of hyaluronidase drug products containing mammalian hyaluronidase enzyme preparations that have certain functional characteristics (i.e., in vitro enzymatic activity as established through USP or National Formulary

¹ Official Monographs, Hyaluronidase Injection and Hyaluronidase for Injection, USP 26.

assay). Hyaluronidase was found to be effective for three indications: 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 DESI review and findings were not limited to the efficacy of Wydase alone; the findings applied to Searle's Alidase and Abbott's Hyazyme, as well as other identical, related, and similar hyaluronidase drug products that entered the market based upon the DESI findings. At one time there were 10 legally marketed hyaluronidase products with NDAs.

II. Safety and Effectiveness of Hyaluronidase Drug Products

A new drug may be approved if the applicant provides adequate evidence demonstrating the drug's safety and effectiveness as required by the Act. Section 505(b)(1)(A) of the Act (21 U.S.C. 355(b)(1)(A)) requires an NDA to contain "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." An application described in section 505(b)(2) of the Act is considered to be submitted under section 505(b)(1) and also must contain adequate evidence of safety and effectiveness. However, a 505(b)(2) application may rely for approval on investigations that were not conducted by or for the 505(b)(2) applicant and to which the applicant has not obtained a right of reference. The data to support the safety and/or effectiveness for the drug product in the 505(b)(2) application may be derived wholly, or in part, from published reports of studies conducted by someone other than the applicant or from an earlier Agency finding of safety and effectiveness for the drug.

You ask that FDA recognize that the sponsors of any NDA for a hyaluronidase drug product cannot satisfy the requirements of section 505(b) of the Act to demonstrate the safety and effectiveness of their product unless (1) the sponsor conducts clinical trials to show safety and effectiveness, (2) the new product is shown to be equivalent to Wydase, or (3) the finished drug product uses an identical raw material source and a comparable production process to Wydase.² FDA has concluded that none of these conditions is necessary for FDA to determine that hyaluronidase drug products are safe and effective.

A. Effectiveness

As indicated previously, the DESI review of hyaluronidase products (including Wydase, Alidase, and Hyazyme) found these products to be effective for certain indications. The DESI findings continue to be supported by recent literature.³ The efficacy of these products, as described in the

² We note that bioequivalence to Wydase is not a requirement for the approval of a hyaluronidase NDA (21 U.S.C. 355(b)).

³ Guise P. Laurent. *Sub-Tenon's Block: The Effect of Hyaluronidase on Speed of Onset and Block Quality*, *Anaesth Intensive Care*. 1999; 27: 179-181. Alwitry A, Chaudhary S, Gopee K, Butler TKH, Holden, R. *Effect of*

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DESI determination, relates to the in vitro enzymatic activity of hyaluronidase. There is a current USP in vitro assay that is used to determine the number of USP hyaluronidase units for a specific product.⁴ This assay directly measures the ability of hyaluronidase to depolymerize HA. Standardized HA is used in the test. This test has been used for over 30 years. It is a direct measure of the activity corresponding to the desired activity for clinical effect.

We have reviewed the relevant information and find that, when considered together with the DESI efficacy determination for hyaluronidase and subsequent confirming literature, the USP functional assay test used to determine the number of USP hyaluronidase units is a valid surrogate for enzymatic activity, and thus may be used to establish the effectiveness of new hyaluronidase products (1) for use as an adjuvant to increase the absorption and dispersion of other injected drugs, (2) for hypodermoclysis, and (3) as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. Clinical effectiveness for these indications is based on the ability of hyaluronidase to break down (depolymerize) HA in the body, thereby allowing a co-administered product to flow into the surrounding tissue. Because the product is administered directly at the site of action, a direct measure of the desired activity is the most sensitive measure of effectiveness available for these indications. Therefore, we find that additional clinical studies of the effectiveness of new hyaluronidase drug products are not needed to establish effectiveness for these indications.

Your petition lists other indications for which effectiveness has not been established. We note, for example, that the use of hyaluronidase to clear vitreous hemorrhages is not an approved indication. We also note that hyaluronidase is not approved for any of the other "less well-established" clinical uses you list. For a hyaluronidase drug product to list any of these uses as approved indications, data and information to support these indications would need to be submitted to FDA and approved.

Your petition suggests that the source of the hyaluronidase is important to establishing the effectiveness of the product. According to your citizen petition, Wydase is sourced from bovine testicular tissue. The DESI findings upon which the efficacy determination for Wydase was based established the clinical usefulness of hyaluronidase drug products containing mammalian

Hyaluronidase on Ocular Motility in Sub-Tenon's Anesthesia, J Cataract Refract Surg. 2002; 28: 1420-1423. Moharib MM, Mitra S, Rizvi SG. *Effect of Alkalinization and/or Hyaluronidase Adjutancy on a Local Anesthetic Mixture for Sub-Tenon's Ophthalmic Bloc*, Acta Anaesthesiol Scand. 2002; 46: 599-602. Rowley SA, Hale JE, Finlay RD. *Sub-Tenon's Local Anaesthesia: The Effect of Hyaluronidase*, Br J Ophthalmol. 2000; 84: 435-436. House PH, Hollands RH and Schulzer M. *Choice of Anesthetic Agents for Peribulbar Anesthesia*, J Cataract Refract Surg. 1991; 17:80-83. Morsman CD and Holden R. *The Effects of Adrenaline, Hyaluronidase and Age on Peribulbar Anaesthesia*, Eye. 1992; 6:290-292. Mantovani C, Bryant AE and Nicholson G. *Efficacy of Varying Concentrations of Hyaluronidase in Peribulbar Anaesthesia*, Br J Anaesthesia. 2001; 86(6): 876-878.

⁴ See footnote 1, supra.

hyaluronidase preparations without specifying species source.⁵ The literature on the effectiveness of hyaluronidase products addresses products of both bovine and ovine sources.⁶ The USP makes no distinction between the different animal sources of testicular hyaluronidases; it groups all mammalian testicular hyaluronidases together in the monographs for hyaluronidase (hyaluronidase for injection and hyaluronidase injection).⁷ Therefore, we find that the specific mammalian testicular source of hyaluronidase for injection USP does not affect the effectiveness of a hyaluronidase product when the potency is established through use of the assay discussed above.

Your petition states that the published literature does not provide a basis for the selection of an appropriate dosing regimen for the use of a new hyaluronidase product in ophthalmic anesthesia. You state that your review of the literature does not show a consensus as to the dose of hyaluronidase that should be added to the anesthetic or anesthetics used in ophthalmic surgery, and that the lack of any dose-response data in published controlled studies does not allow a new product to reference those studies for dosing information on labeling. You also state that, with a product such as hyaluronidase, clinical dose-ranging data are required to determine the optimal dose of a new drug product before that product can be approved for use as a spreading agent for other co-administered drugs. (Petition at 13)

The literature supports a dosing regimen for the use of a new hyaluronidase drug product in the range of 50 to 300 units per milliliter.⁸ The use of the USP functional assay test provides for a

⁵ Briefing letter, Department of Health, Education, and Welfare, from Henry E. Simmons, M.D., to Charles C. Edwards, M.D., Commissioner of Food and Drugs, DESI announcement 6343: Hyaluronidase, August 11, 1970.

⁶ Britton RC and Habif DV. *Clinical Uses of Hyaluronidase, Surgery*. 1953; 33:917-942. Burket LC and Gyorgy P. *Clinical Observations on Use of Hyaluronidase*, Pediatrics 1949; 3:56-63. Jaworski AA and Farley JE. *Hyaluronidase in Administration of Fluids*, Amer J Dis Child. 1950; 79:59-64. Alwitry A, Chaudhary S, Gopee K, Butler TKH, Holden, R. *Effect of Hyaluronidase on Ocular Motility in Sub-Tenon's Anesthesia*, J Cataract Refract Surg. 2002; 28: 1420-1423. Moharib MM, Mitra S, Rizvi SG. *Effect of Alkalinization and/or Hyaluronidase Adjutancy on a Local Anesthetic Mixture for Sub-Tenon's Ophthalmic Bloc*, Acta Anaesthesiol Scand. 2002; 46: 599-602. Rowley SA, Hale JE, Finlay RD. *Sub-Tenon's Local Anaesthesia: The Effect of Hyaluronidase*, Br J Ophthalmol. 2000; 84: 435-436.

⁷ Official Monographs, Hyaluronidase Injection and Hyaluronidase for Injection, USP 26. The USP began development of the monograph for hyaluronidase for injection in the early 1950s. To begin the early phase of the monograph, an international conference was held. In attendance were representatives of hyaluronidase manufacturers, as well as representatives from the American Medical Association, academic laboratories, the World Health Organization (WHO), and the FDA. After the conference, a USP panel was formed to develop the monograph. Panel members included representatives from industry, FDA, and WHO. This monograph became official in 1955 and grouped the mammalian testicular-sourced products of hyaluronidase together. This characterization continues today. USP 26 defines hyaluronidase for injection as a "sterile, dry, soluble, enzyme product, prepared from mammalian testes...."

⁸ Hechter, O et al. *The Clinical Use of Hyaluronidase in Hypodermoclysis*, J Pediatrics. 1947; 30(6): 645-656. Cella LJ, Means JA. *Clinical Significance of Hyaluronidase*, Marquette M Review. 1947; 13:14-18. Tassman IS. *The Use of Hyaluronidase in Ophthalmology*, AJO. 1952; 35(5):683-686. Hinman F. *Hyaluronidase in Excretory*

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mechanism in which equivalent numbers of USP hyaluronidase units will be administered as described in the literature. This dosing is consistent with NDAs previously approved for hyaluronidase, including Wydase.

B. Safety

Hyaluronidase injection and hyaluronidase for injection products have been safely used and marketed for over 50 years. The safety of different formulations and sources of hyaluronidase is described in the literature beginning in the 1940s.⁹ Additionally, our review of adverse events for hyaluronidase products with different formulations and from different sources has revealed very few adverse events.

The principal documented safety concern associated with hyaluronidase products has been the potential of the products to cause allergic reactions. Our review of the existing literature has not identified specific safety problems attributable to any particular mammalian source for this product. Therefore, we do not believe the allergic potential of these products is source-specific.

To better ensure human safety, the Agency intends to require sponsors to conduct appropriate clinical studies to further assess the allergic potential of these products, if human safety data on the specific product are not otherwise available. For hyaluronidase products for which there is no product-specific data on human exposure or for changes that occur in the source or manufacturing process, we will require that allergic potential be evaluated using either a dosing regimen, as described in the labeling for hyaluronidase, or a skin test using an intradermal injection.

Preparations of hyaluronidase marketed to date have not been highly purified. Typically, more than 50 percent by mass of the drug substance is nonhyaluronidase, source-derived material. All forms of the hyaluronidase enzyme from mammalian sources will include many nonhyaluronidase proteins that may have the capacity to act in a manner that induces an allergic reaction. Because we do not know which specific protein contaminants in any current or future products might have an allergic potential, adequate standards for manufacturing are necessary to ensure consistency with the product used in the tests for allergenic potential. For all new drug applications for these products, we require careful review of the manufacturing of the drug

Urography, Arch Surgery. 1951; 63(5): 585. Hechter O. *Reconstitution of the Dermal Barrier to Fluid Diffusion Following Administration of Hyaluronidase*, Proc Soc Exp Biol Med. 1948; 67:343-344.

⁹ Hechter, O et al. *The Clinical Use of Hyaluronidase in Hypodermoclysis*, J Pediatrics. 1947; 30(6): 645-656.

Cella LJ, Means JA. *Clinical Significance of Hyaluronidase*, Marquette M Review. 1947; 13:14-18. Hechter O. *Reconstitution of the Dermal Barrier to Fluid Diffusion Following Administration of Hyaluronidase*, Proc Soc Exp Biol Med. 1948; 67:343-344. *The Biologic Significance of Hyaluronidase*, JAMA. 1947; 135(5): 289.

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substance and the drug product. This includes review of the hyaluronidase source material, its handling, and its processing.

Hyaluronidase drug products, including Wydase, have been labeled to alert health professionals to the possibility of allergic reactions, and we will continue to require this labeling.

You state in your petition that (1) bovine and ovine hyaluronidase clearly differ in their characteristics, (2) safety data is specific to the source species, and (3) because the existing literature does not indicate the source of hyaluronidase used, this safety data cannot be applied to any new product sourced from a different species. However, the article you submitted to support your assertion demonstrates that bovine and ovine hyaluronidases have essentially the same characteristics.¹⁰ In your petition you request that the Agency require an "identical raw material" source and a comparable production process to that used for Wydase for any new hyaluronidase drug product. We note that neither the species source used nor any specific production process was required for any of the approved hyaluronidase drug products, including Wydase.

You state that safety data derived from local tissue infiltration is not necessarily the same as that derived from systemic administration. We agree. However, hyaluronidase drug products are not approved for systemic administration. The labeling for Wydase indicates that it is "not recommended for IV use" and that the drug product's activity is inactivated by components present in the blood. Therefore, it is unlikely that hyaluronidase approved for local application would be used systemically. Before hyaluronidase could be approved for any systemic use, an NDA containing adequate data demonstrating safety and effectiveness of this use would be required.

While you state that Wydase has demonstrated an acceptable safety profile based on your review of spontaneous adverse events, we note that your reference 19 simply states, "Data on file with Baxter Healthcare," and therefore provides no data for FDA to review.

III. Conclusions

In your petition, you have made several assertions regarding what should be required to demonstrate the safety and effectiveness of hyaluronidase. Whether or not your suggestions might be appropriate for other drug products, particularly if a sponsor were trying to demonstrate the interchangeability of two products, they are not necessary for approval of hyaluronidase products. The effectiveness and safety of hyaluronidase products can be established based upon (1) the efficacy determination under the DESI process, (2) subsequent literature confirming the

¹⁰ See reference 7 submitted with your petition, Krishnapillai AM, Anthony Taylor KE et al, *Characterization of Norway Lobster (Nephrops Norvegicus) Hyaluronidase and Comparison with Sheep and Bovine Testicular Hyaluronidase*, Food Chemistry. 1999; 65(4):520.

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effectiveness of hyaluronidase for certain uses, (3) an in vitro assay that has been established as an effective and reliable surrogate for desired clinical effect, (4) human safety data described in the literature from years of experience with marketed products, and (5) limited clinical testing to ascertain the allergenic potential of specific products. Accordingly, we do not believe that the conditions you suggest are necessary for FDA to approve an application for hyaluronidase drug products under section 505(b)(2) of the Act.

A determination of efficacy for mammalian testicular-derived hyaluronidase drug products was made in the DESI review as described in the published *Federal Register* notice (35 FR 14800). After a review of the scientific literature and the studies identified in your petition, we have not found any evidence that raises new questions about the effectiveness of hyaluronidase products. Effectiveness for indications not currently approved would need to be supported by adequate data.

The scientific literature provides extensive evidence of the safety of hyaluronidase drug products in humans based on many years of use of marketed products. In addition, in the absence of other clinical safety data for a specific product, we will require limited clinical safety testing of each product to address its allergenic potential. Safety will be confirmed in a manner that will satisfy the Agency that the expected allergic reaction rate is unlikely to exceed a rate observed in historically marketed products (an allergic reaction rate of less than 10 percent). This may be accomplished in clinical trials or by the monitored administration of the drug product in its proposed final form. We also will require adequate standards for manufacturing to ensure consistency with the tested products.

For the reasons discussed above, your petition is denied.

Sincerely,



Steven K. Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research