

I.V. Systems/Medical Products

Baxter Healthcare Corporation
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Baxter

October 24, 2003

BY HAND DELIVERY

Dockets Management Branch (HFA 305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, Maryland 20852

2216 03 OCT 24 P 1:19

Re: Wydase® (hyaluronidase)

CITIZEN PETITION

Dear Sir or Madam:

The undersigned submits this petition under section 505(b) the Federal Food, Drug, and Cosmetic Act (FDC Act) (21 U.S.C. § 355(b)) and 21 C.F.R. § 10.30 to request the Commissioner of Food and Drugs determine that the Food and Drug Administration (FDA) will not approve any new drug application (NDA) for a hyaluronidase product unless the conditions set forth in this petition are satisfied.

Baxter Healthcare Corporation (Baxter) is the current holder of NDA 06-343 for hyaluronidase (Wydase®), which was discontinued in 2000 by the previous owner of this NDA, Wyeth. 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 is currently working to resume production of Wydase®. Resumption of production of Wydase® is particularly important, as ophthalmologists have reported an increased incidence of postoperative complications, including permanent diplopia and ptosis, when hyaluronidase is not used. This has resulted in some ophthalmologists using hyaluronidase compounded by pharmacies(1).

2003P.0494

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A. Action Requested.

Petitioner asks that the Commissioner determine that FDA will not approve any new drug application (NDA) for a hyaluronidase product unless the conditions set forth in this petition are satisfied.

B. Statement of Grounds.

Baxter, as holder of the NDA for Wydase®, believes:

1. Wydase®'s safety and efficacy have been demonstrated by over 50 years of clinical use.
2. Naturally occurring hyaluronidases are a heterogeneous family of glycoprotein enzymes with different amino acid sequences and species-specific glycosylation, different kinetics and different sites of hyaluronic acid cleavage making the efficacy and tolerability of each potential product unique and defined both by the raw material source and the production process.
3. The safety and efficacy of Wydase® cannot be extrapolated to any other hyaluronidase product unless that product utilizes the same enzyme source and the same production process as Wydase®.

Therefore, the safety and efficacy of any new hyaluronidase product must:

1. Be proven by adequately designed and powered clinical trials. There is significant potential for immunologic adverse events resulting from administration of a complex biological mixture (which may be caused by the presence of minor constituents of the mixture or differences in protein amino acid sequence or glycosylation). Due to the known interspecies variability of immunologic responses and the poor predictive value of preclinical models of immunogenicity, safety of new hyaluronidase products or delivery of the product by a new route of administration (such as periorbital versus intraocular

injection) cannot be assumed and must be demonstrated through properly designed clinical trials; or

2. Be shown to be equivalent to Wydase® as described in appropriately designed and sized published clinical trials through the use of properly validated models demonstrating comparable pharmacokinetics, pharmacodynamics and safety in human tissue; or
3. 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 be shown to be fully equivalent to Wydase®.

Hyaluronidase is a naturally occurring family of enzymes that hydrolyze hyaluronic acid, a polysaccharide constituent of both organs and body fluids. Its activity was first identified as a "spreading factor" in extracts from mammalian testes in 1928(2). It is an endogenous protein and serves a multitude of functions ranging from activity as a degradative enzyme in the remodeling of cartilage to facilitating sperm penetration of the zona pellucida during oocyte fertilization(3). Hyaluronidase and hyaluronic acid are also involved in pathogenic processes like malignant transformation and tumor progression(4). Hyaluronidase is also produced by a number of pathogenic bacteria including Streptococci, Staphylococci and Bacteroides where it most likely facilitates tissue invasion. It is also found in a variety of toxic animal venoms where it appears to be a naturally occurring spreading agent for venoms(5).

Hyaluronidase structure and specific function can be highly variable. Specific sites of hyaluronidase cleavage of hyaluronic acid vary by species: bacterial, bee venom and human hyaluronidase can be distinguished by the specific bonds cleaved(6). Bovine and ovine testicular hyaluronidases clearly differ in their characteristics, particularly with regard to naturally occurring inhibitors(7). Hyaluronidase within a given species also

varies by location: in humans for example, plasma hyaluronidase (Hyal-1) displays only 40% homology to sperm-specific hyaluronidase (PH-20) (6).

Hyaluronidase preparations have a variety of potential clinical applications. The currently approved hyaluronidase product in the United States, Wydase®, is indicated as an adjuvant to increase absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents(8). In perhaps the most common clinical application, Wydase® has been used as an adjunct in local ophthalmic anesthesia, specifically retrobulbar, sub-Tenon's and periorbital blocks. Hyaluronidase may also be efficacious in accelerating clearance of vitreous hemorrhage by transiently liquefying the vitreous humor and has been preliminarily studied as a potential treatment for diabetic retinopathy(9).

Other, less well-established clinical uses for hyaluronidase include myocardial sparing in ischemia-reperfusion injury(10), treatment of ganglion cysts(11), and reduction of paraphimosis(12). Systemic hyaluronidase had also been reported to accelerate passage of antibiotics from the circulation into synovial fluid(6). Hyaluronidase has been investigated for use as an adjuvant in local and systemic cancer therapy to increase penetration of chemotherapeutic agents in preclinical models(13,14) and a pilot study in children with malignant brain tumors (n=19) showed a significantly improved outcome for the hyaluronidase treated group than for historic controls(15). Hyaluronidase has also been investigated in preclinical transplantation studies and has been shown to decrease intragraft pressure in rejection of transplanted rat hearts(16).

The hyaluronidase source for Wydase® is bovine testicles. The raw material is processed and formulated in a specific process as delineated in the approved NDA to manufacture Wydase®. Wydase® differs from scientific-grade hyaluronidase in having a proprietary purification step to remove additional bovine proteins. The most frequent contaminants found in less pure bovine testicular hyaluronidase express proteolytic and glucuronidase activity(6).

In August 2003, ISTA Pharmaceuticals, Inc. (ISTA) filed a New Drug Application (NDA) for its ovine-sourced hyaluronidase, Vitrase®, for use as “a spreading agent to facilitate the dispersion and absorption of other drugs.” According to the August 2003 press release from ISTA, no additional studies had been conducted. ISTA had previously filed a NDA (21-414) in December 2002 for Vitrase® for treatment of vitreous hemorrhage supported by clinical trials with intraocular use in that indication. Due to the species-specific as well as the intraspecies, site-specific variability of hyaluronidases, this product clearly differs from the bovine-derived product, Wydase®, already approved in the United States.

Baxter believes that, for a new hyaluronidase product, sourced from a different species and manufactured by a different process, to be approved as a spreading agent for other drugs, it must demonstrate safety and efficacy as well as define appropriate dosing in that indication and cannot rely on the Agency’s finding of safety and effectiveness of the approved product, Wydase®. We also believe there is inadequate published literature on hyaluronidase preparations sufficiently similar to these new products to support approval.

We do not believe it is possible for any other hyaluronidase formulation to demonstrate bioequivalence to Wydase® for a particular application based solely on previously published studies or studies with the product in other unapproved applications. As noted in a presentation by Dena Dixon, MD, Associate Director of Medical Affairs, Office of Generic Drugs, FDA, titled “Clinical Endpoint Bioequivalence Studies for Locally Acting Drugs,” “PK studies are not adequate” for locally-acting drugs and “Most require clinical endpoint studies”(17).

Wydase® is a complex biological product whose final composition has not been totally characterized and is thus determined by both the raw material and the manufacturing process. While hyaluronidase is the major active component, there may be minor components that contribute to the safety and efficacy it has shown in over 50

years of clinical use. This efficacy has been confirmed by the Drug Efficacy Study Implementation (DESI) program findings published in the Federal Register(18). This finding of efficacy can only be extrapolated to a new product if that product utilizes the same raw material source and the same manufacturing process as one of the assessed products (Wydase® [Wyeth Laboratories, Inc, now held by Baxter], Alidase® [G.D. Searle and Company] or Hyazyme® [Abbott Laboratories]) to insure equivalent activity and tolerability.

- I. **Safety:** The published literature does not provide adequate information for *a priori* assessment of the safety of a new hyaluronidase product. The safety information available from the 1377 patients enrolled in the 16 controlled trials with a primary endpoint of hyaluronidase efficacy consists primarily of generalized statements that few significant events were seen. Adverse events are not specifically identified and cannot be quantitated so that they can be compared to the known safety database for Wydase®. Without such information, no risk/benefit analysis of a new product compared to Wydase® can be done without adequately designed and powered clinical trials.

As previously noted, the structure and activity of hyaluronidase varies by species, as will the presence and nature of minor components with potential biological and immunological activity. Thus, safety data is specific to the source species as well as being specific for the production process of a new product. The majority of the clinical trials reviewed do not indicate the source of hyaluronidase utilized in the study. As such, it is impossible to determine if the data generated in those studies is in any manner relevant to a new product. Without this information, the safety data present in the literature cannot be applied to any new product.

Any biological product may cause immunologically mediated adverse events. The potential for these events is related both to the source of hyaluronidase as well as the process by which the final product is made. The approved labeling for Wydase®(8) notes, "A preliminary test for sensitivity should be conducted." "Allergic reactions (urticaria, angioedema) are rare. Anaphylactic-like reactions following retrobulbar or intravenous injections have occurred. Cardiac fibrillation has been encountered once." Unfortunately, preclinical models are not always predictive of immunogenicity. Spontaneous reporting of adverse events, including potentially immunologically mediated events, for Wydase® from 1986 to 2003 has demonstrated an acceptable safety profile in general use(19).

As previously noted, published literature on hyaluronidase does not contain adequately specific information to allow a quantitative assessment of safety and any risk/benefit comparison to Wydase®. Immunogenic safety is product specific and the exact product used in published studies is infrequently identified. Thus, the immunologic safety information from published studies cannot be extrapolated to a specific product unless those studies were done with that particular product.

Similarly, safety data from controlled clinical trials with other sites of application, either intraorbital or systemic, cannot be extrapolated to local tissue infiltration. From an immunologic perspective, the intraorbital vitreous humor is relatively sequestered when compared to percutaneous administration. Systemic exposure as well is very likely to have a different safety and immunologic profile.

There is also the potential that any new hyaluronidase would be used outside of approved labeling, so a new product that was approved for local

application would likely be used systemically as well. Wydase® has been approved and used for over 50 years. The database of spontaneously reported adverse events (19) includes all uses of Wydase. The safety profile is acceptable and any new product would need to demonstrate equivalent safety in all uses, local and systemic, to be considered equivalent to Wydase® in safety.

- II. **Efficacy:** The published literature does not provide sufficient information to permit determination of efficacy or proper dosing for a new hyaluronidase product. As the most common use of hyaluronidase is in ophthalmic anesthesia, we conducted a review of published clinical trials of hyaluronidase use from the first report in 1949 to the present and discovered conflicting efficacy results. Of 88 publications found on literature search where hyaluronidase has been used with ophthalmic anesthesia in a clinical trial (20-106), only 22 studies in 21 publications have defined hyaluronidase efficacy as the primary efficacy endpoint. Six of these studies were considered uninterpretable for efficacy (Table 1):

Table 1
Studies Uninterpretable for Efficacy

Author	n	Reason
Atkinson(20)	109	No raw data, conclusion based on "impression"
Barr(21)	24	Pharmacokinetic study only
Bjornstrom(22)	54	Open, 2-arm study with 2 variables: hyaluronidase & epinephrine
Dutton(23)	24	Open, uncontrolled study with 100% success rate
Hagan(1)	100	Compounded hyaluronidase versus Wydase: No differences
Savela, Study 2(24)	80	No difference between 2 active arms: hyaluronidase 7.5 & 15 IU/mL

The remaining 16 studies enrolled a total of 1377 patients, 988 patients in studies supportive of efficacy and 389 patients in studies not supportive of efficacy (Table 2). Of these studies, three were done with Hyalase® (Wyeth), one with Wydase® (Wyeth), one with Hyason® (Organon) and the remaining 11 did not specify the hyaluronidase source, limiting their applicability to any new formulation of hyaluronidase. Doses used in the nine positive and seven negative studies ranged from 7.5 to 150 IU/mL.

Table 2
Studies Interpretable for Efficacy

Positive			Negative		
Author	n	Dose	Author	n	Dose
Sarvela Study 1(24)	70	7.5 IU/mL	Mindel(33)	27	7.5 IU/mL
Roberts(25)	100	10 U/mL	Mather(34)	40	15 IU/mL
Nicoll(26)	100	15 IU/mL	Moharib(35)	60	15 IU/mL
Thomson(27)	150	15 IU/mL	Prosser(36)	50	25 IU/mL
Guise(28)	120	30 IU/mL	Crawford*(37)	60	50 U/mL
Rowley(29)		30 IU/mL	Brydon(38)	60	50 & 150 IU/mL
House(30)	117	50 IU/mL	Bowman*(39)	92	150 IU/mL
Morsman*(31)	91	50 IU/mL			
Mantovani(32)	90	15 & 150 IU/mL			

*Randomized but open studies

The selection of clinically meaningful endpoints for the demonstration of efficacy is critical. While a one-minute decrease in time to onset of anesthesia or akinesia may be statistically significant, it is not truly clinically meaningful. The real measure of clinical benefit is determined by the quality of the block: is akinesia adequate for the surgeon and is analgesia adequate for the patient? When these criteria are used, only seven

of the studies are positive while eight are negative (Table 3). One study specifically did not address the adequacy of anesthesia(34). There is little mention of any validation of this endpoint in any of the published studies.

Table 3
Studies Interpretable for Efficacy
Quality of Block

Positive (7)	Negative (8)
Thomson*(27)	Guise(28)
Sarvela, Study 1(24)	Mantovani(32)
House*(30)	Crawford(37)
Roberts*(25)	Prosser(36)
Rowley*(29)	Brydon(38)
Morsman(31)	Moharib(35)
Nicoll(26)	Mindel(33)
	Bowman*(39)

*Anesthetic Included epinephrine

Mather study(34) excluded quality of block

This variability in outcomes shows that demonstrating efficacy in this indication is challenging and cannot be assumed. There are a number of confounding variables that contribute to the mixed results for efficacy:

- A. **Source of Hyaluronidase:** As previously noted, hyaluronidase from different species, or even within the same species, differs in specificity and activity. This might be compounded by differences in activity related to distinct production processes.

- B. **Type of Block:** Hyaluronidase efficacy may be related to the type of anesthetic block utilized in the study: retrobulbar, peribulbar or sub-Tenon's.
- C. **Volume of Anesthetic Injected:** Those studies that document volume of anesthetic injected usually fall within 5 and 10 mL. Physiologically, the larger the amount of anesthetic injected the more likely rapid, adequate anesthesia and akinesia will be achieved.
- D. **Anesthesia pH:** The studies show conflicting results concerning pH adjustment of the anesthetic mixture. One study(25) noted pH adjustment and hyaluronidase together were superior to either alone while another(35) noted no improvement with pH adjustment of the anesthetic mixture prior to use.
- E. **Use of Epinephrine:** A small (n=24) pharmacokinetics study in peribulbar block showed that added epinephrine altered the systemic kinetics of lidocaine and bupivacaine but added hyaluronidase did not have the same effect(21). Physiologically, vasoconstriction by epinephrine could easily alter the efficacy of any topical anesthetic solution, whether or not it contained hyaluronidase. Of particular interest are those studies with an endpoint of the quality of the block. Four of seven (57%) positive studies utilized epinephrine while only one of eight of the negative studies (13%) used it.
- F. **Anesthetic Agents Used:** While most of the interpretable studies utilized lidocaine and bupivacaine, concentrations of those agents varied. Other agents used included etidocaine, mepivacaine and bupivacaine alone. As the pharmacodynamics of these anesthetic agents are markedly different, differences in efficacy could result.

- G. **Type of Surgical Procedure:** Many studies mix different ophthalmic surgical procedures that could easily affect analgesic efficacy. Length of procedures also is a variable that could easily affect measures of analgesia and akinesia.
- H. **Skill of Anesthesiologist:** With local anesthesia, location of the injected anesthetic solution relative to the nerves being blocked could have a clear effect on overall efficacy as well as time to onset of anesthesia.
- I. **Sample Sizes:** Many of the interpretable studies are small, with sample sizes ranging from 27 to 150 patients. Numerical differences that are not statistically significant in small studies could become so with larger sample sizes.
- J. **Potential Bias:** While most of the studies were double-blind, three were randomized but open, one positive(30), and two negative(37,39) allowing potential bias.

The variability in study design, anesthetic agents utilized, hyaluronidase preparation utilized and endpoints is too large to allow for statistically meaningful interpretation of efficacy seen in these studies. With such variability, techniques such as meta-analysis cannot be applied.

The efficacy and dosing of Wydase® as an adjunct for ophthalmic anesthesia has been established in over 50 years of clinical use and confirmed by the DESI program review(18). Baxter believes that much of the inconsistency in efficacy results in the published literature is due to the previously noted confounding variables. Thus, it is possible for a new hyaluronidase product to demonstrate efficacy only through well designed, adequately powered clinical trials using a validated, clinically meaningful endpoint.

III. Dosing Regimen: The published literature does not provide a basis for selection of an appropriate dosing regimen for the use of a new hyaluronidase product in ophthalmic anesthesia. A review of the 88 published reports of clinical trials of hyaluronidase use in ophthalmologic anesthesia shows no consensus as to the dose of hyaluronidase that should be added to the anesthetic(s). Doses used in published studies for ophthalmologic anesthesia range from 3.75 IU/mL to 300 IU/mL. For the 16 studies interpretable for efficacy in this indication, the nine positive studies and seven negative studies used doses ranging from 7.5-150 IU/mL. The lack of any dose response in published controlled studies does not allow a new product to reference them for dosing information for labeling.

While pharmacokinetics might be used to show dose equivalence for two intravenous products, there is no equivalent bioassay for local tissue administration. With a biological product such as hyaluronidase, clinical dose ranging data are required to determine the optimal dose of a new product with a new source and new manufacturing process before that product can be approved for use as a spreading agent for other coadministered drugs.

Thus, approval of any new hyaluronidase product requires that the new product demonstrate the dosing, safety and efficacy that would be specific for that product and that method of administration, data that would need to be generated with adequately designed and sized clinical trials or by demonstrating that the new product is analytically identical to Wydase® and has the same pharmacokinetic and pharmacodynamic characteristics as Wydase® in local tissue applications.

C. *Environmental Impact.*

The Petitioner claims a categorical exclusion under 21 C.F.R. § 25.31(a) and (g).

D. *Economic Impact.*

The petitioner will submit economic impact information upon request of the Commissioner.

E. *Certification*

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies and that it includes representative data and information known to the petitioner that are unfavorable to the petitioner.

Dated: October 24, 2003

Respectfully submitted,



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
908-286-7304

Attachments

I.V. Systems/Medical Products

Baxter Healthcare Corporation
Kent S. Allenby, M.D., FACP
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New Providence, New Jersey 07974
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2236 '03 OCT 27 P4:17

October 24, 2003

Dockets Management Branch (HFA 305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061 (HFA 305)
Rockville, Maryland 20852

Re: Wydase® (hyaluronidase)

Dear Sir or Madam:

On Friday, October 24, 2003 Baxter Healthcare submitted a facsimile copy of a Citizen Petition for Wydase® (hyaluronidase). Attached is the original copy.

Sincerely,

A handwritten signature in black ink, appearing to read 'KS Allenby', written over the typed name.

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
908-286-7304



October 24, 2003

BY HAND DELIVERY

Dockets Management Branch (HFA 305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061 (HFA-305)
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2237 '03 OCT 27 P4:19

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The undersigned submits this petition under section 505(b) the Federal Food, Drug, and Cosmetic Act (FDC Act) (21 U.S.C. § 355(b)) and 21 C.F.R. § 10.30 to request the Commissioner of Food and Drugs determine that the Food and Drug Administration (FDA) will not approve any new drug application (NDA) for a hyaluronidase product unless the conditions set forth in this petition are satisfied.

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A. Action Requested.

Petitioner asks that the Commissioner determine that FDA will not approve any new drug application (NDA) for a hyaluronidase product unless the conditions set forth in this petition are satisfied.

B. Statement of Grounds.

Baxter, as holder of the NDA for Wydase®, believes:

1. Wydase®'s safety and efficacy have been demonstrated by over 50 years of clinical use.
2. Naturally occurring hyaluronidases are a heterogeneous family of glycoprotein enzymes with different amino acid sequences and species-specific glycosylation, different kinetics and different sites of hyaluronic acid cleavage making the efficacy and tolerability of each potential product unique and defined both by the raw material source and the production process.
3. The safety and efficacy of Wydase® cannot be extrapolated to any other hyaluronidase product unless that product utilizes the same enzyme source and the same production process as Wydase®.

Therefore, the safety and efficacy of any new hyaluronidase product must:

1. Be proven by adequately designed and powered clinical trials. There is significant potential for immunologic adverse events resulting from administration of a complex biological mixture (which may be caused by the presence of minor constituents of the mixture or differences in protein amino acid sequence or glycosylation). Due to the known interspecies variability of immunologic responses and the poor predictive value of preclinical models of immunogenicity, safety of new hyaluronidase products or delivery of the product by a new route of administration (such as periorbital versus intraocular

injection) cannot be assumed and must be demonstrated through properly designed clinical trials; or

2. Be shown to be equivalent to Wydase® as described in appropriately designed and sized published clinical trials through the use of properly validated models demonstrating comparable pharmacokinetics, pharmacodynamics and safety in human tissue; or
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varies by location: in humans for example, plasma hyaluronidase (Hyal-1) displays only 40% homology to sperm-specific hyaluronidase (PH-20) (6).

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We do not believe it is possible for any other hyaluronidase formulation to demonstrate bioequivalence to Wydase® for a particular application based solely on previously published studies or studies with the product in other unapproved applications. As noted in a presentation by Dena Dixon, MD, Associate Director of Medical Affairs, Office of Generic Drugs, FDA, titled “Clinical Endpoint Bioequivalence Studies for Locally Acting Drugs,” “PK studies are not adequate” for locally-acting drugs and “Most require clinical endpoint studies”(17).

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years of clinical use. This efficacy has been confirmed by the Drug Efficacy Study Implementation (DESI) program findings published in the Federal Register(18). This finding of efficacy can only be extrapolated to a new product if that product utilizes the same raw material source and the same manufacturing process as one of the assessed products (Wydase® [Wyeth Laboratories, Inc, now held by Baxter], Alidase® [G.D. Searle and Company] or Hyazyme® [Abbott Laboratories]) to insure equivalent activity and tolerability.

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As previously noted, the structure and activity of hyaluronidase varies by species, as will the presence and nature of minor components with potential biological and immunological activity. Thus, safety data is specific to the source species as well as being specific for the production process of a new product. The majority of the clinical trials reviewed do not indicate the source of hyaluronidase utilized in the study. As such, it is impossible to determine if the data generated in those studies is in any manner relevant to a new product. Without this information, the safety data present in the literature cannot be applied to any new product.

Any biological product may cause immunologically mediated adverse events. The potential for these events is related both to the source of hyaluronidase as well as the process by which the final product is made. The approved labeling for Wydase®(8) notes, "A preliminary test for sensitivity should be conducted." "Allergic reactions (urticaria, angioedema) are rare. Anaphylactic-like reactions following retrobulbar or intravenous injections have occurred. Cardiac fibrillation has been encountered once." Unfortunately, preclinical models are not always predictive of immunogenicity. Spontaneous reporting of adverse events, including potentially immunologically mediated events, for Wydase® from 1986 to 2003 has demonstrated an acceptable safety profile in general use(19).

As previously noted, published literature on hyaluronidase does not contain adequately specific information to allow a quantitative assessment of safety and any risk/benefit comparison to Wydase®. Immunogenic safety is product specific and the exact product used in published studies is infrequently identified. Thus, the immunologic safety information from published studies cannot be extrapolated to a specific product unless those studies were done with that particular product.

Similarly, safety data from controlled clinical trials with other sites of application, either intraorbital or systemic, cannot be extrapolated to local tissue infiltration. From an immunologic perspective, the intraorbital vitreous humor is relatively sequestered when compared to percutaneous administration. Systemic exposure as well is very likely to have a different safety and immunologic profile.

There is also the potential that any new hyaluronidase would be used outside of approved labeling, so a new product that was approved for local

application would likely be used systemically as well. Wydase® has been approved and used for over 50 years. The database of spontaneously reported adverse events (19) includes all uses of Wydase. The safety profile is acceptable and any new product would need to demonstrate equivalent safety in all uses, local and systemic, to be considered equivalent to Wydase® in safety.

- II. **Efficacy:** The published literature does not provide sufficient information to permit determination of efficacy or proper dosing for a new hyaluronidase product. As the most common use of hyaluronidase is in ophthalmic anesthesia, we conducted a review of published clinical trials of hyaluronidase use from the first report in 1949 to the present and discovered conflicting efficacy results. Of 88 publications found on literature search where hyaluronidase has been used with ophthalmic anesthesia in a clinical trial (20-106), only 22 studies in 21 publications have defined hyaluronidase efficacy as the primary efficacy endpoint. Six of these studies were considered uninterpretable for efficacy (Table 1):

Table 1
Studies Uninterpretable for Efficacy

Author	n	Reason
Atkinson(20)	109	No raw data, conclusion based on "impression"
Barr(21)	24	Pharmacokinetic study only
Bjornstrom(22)	54	Open, 2-arm study with 2 variables: hyaluronidase & epinephrine
Dutton(23)	24	Open, uncontrolled study with 100% success rate
Hagan(1)	100	Compounded hyaluronidase versus Wydase: No differences
Savela, Study 2(24)	80	No difference between 2 active arms: hyaluronidase 7.5 & 15 IU/mL

The remaining 16 studies enrolled a total of 1377 patients, 988 patients in studies supportive of efficacy and 389 patients in studies not supportive of efficacy (Table 2). Of these studies, three were done with Hyalase® (Wyeth), one with Wydase® (Wyeth), one with Hyason® (Organon) and the remaining 11 did not specify the hyaluronidase source, limiting their applicability to any new formulation of hyaluronidase. Doses used in the nine positive and seven negative studies ranged from 7.5 to 150 IU/mL.

Table 2
Studies Interpretable for Efficacy

Author	Positive		Author	Negative	
	n	Dose		n	Dose
Sarvela Study 1(24)	70	7.5 IU/mL	Mindel(33)	27	7.5 IU/mL
Roberts(25)	100	10 U/mL	Mather(34)	40	15 IU/mL
Nicoll(26)	100	15 IU/mL	Moharib(35)	60	15 IU/mL
Thomson(27)	150	15 IU/mL	Prosser(36)	50	25 IU/mL
Guise(28)	120	30 IU/mL	Crawford*(37)	60	50 U/mL
Rowley(29)		30 IU/mL	Brydon(38)	60	50 & 150 IU/mL
House(30)	117	50 IU/mL	Bowman*(39)	92	150 IU/mL
Morsman*(31)	91	50 IU/mL			
Mantovani(32)	90	15 & 150 IU/mL			

*Randomized but open studies

The selection of clinically meaningful endpoints for the demonstration of efficacy is critical. While a one-minute decrease in time to onset of anesthesia or akinesia may be statistically significant, it is not truly clinically meaningful. The real measure of clinical benefit is determined by the quality of the block: is akinesia adequate for the surgeon and is analgesia adequate for the patient? When these criteria are used, only seven

of the studies are positive while eight are negative (Table 3). One study specifically did not address the adequacy of anesthesia(34). There is little mention of any validation of this endpoint in any of the published studies.

Table 3
Studies Interpretable for Efficacy
Quality of Block

Positive (7)	Negative (8)
Thomson*(27)	Guise(28)
Sarvela, Study 1(24)	Mantovani(32)
House*(30)	Crawford(37)
Roberts*(25)	Prosser(36)
Rowley*(29)	Brydon(38)
Morsman(31)	Moharib(35)
Nicoll(26)	Mindel(33)
	Bowman*(39)

*Anesthetic Included epinephrine

Mather study(34) excluded quality of block

This variability in outcomes shows that demonstrating efficacy in this indication is challenging and cannot be assumed. There are a number of confounding variables that contribute to the mixed results for efficacy:

- A. Source of Hyaluronidase: As previously noted, hyaluronidase from different species, or even within the same species, differs in specificity and activity. This might be compounded by differences in activity related to distinct production processes.

- B. **Type of Block:** Hyaluronidase efficacy may be related to the type of anesthetic block utilized in the study: retrobulbar, peribulbar or sub-Tenon's.
- C. **Volume of Anesthetic Injected:** Those studies that document volume of anesthetic injected usually fall within 5 and 10 mL. Physiologically, the larger the amount of anesthetic injected the more likely rapid, adequate anesthesia and akinesia will be achieved.
- D. **Anesthesia pH:** The studies show conflicting results concerning pH adjustment of the anesthetic mixture. One study(25) noted pH adjustment and hyaluronidase together were superior to either alone while another(35) noted no improvement with pH adjustment of the anesthetic mixture prior to use.
- E. **Use of Epinephrine:** A small (n=24) pharmacokinetics study in peribulbar block showed that added epinephrine altered the systemic kinetics of lidocaine and bupivacaine but added hyaluronidase did not have the same effect(21). Physiologically, vasoconstriction by epinephrine could easily alter the efficacy of any topical anesthetic solution, whether or not it contained hyaluronidase. Of particular interest are those studies with an endpoint of the quality of the block. Four of seven (57%) positive studies utilized epinephrine while only one of eight of the negative studies (13%) used it.
- F. **Anesthetic Agents Used:** While most of the interpretable studies utilized lidocaine and bupivacaine, concentrations of those agents varied. Other agents used included etidocaine, mepivacaine and bupivacaine alone. As the pharmacodynamics of these anesthetic agents are markedly different, differences in efficacy could result.

- G. **Type of Surgical Procedure:** Many studies mix different ophthalmic surgical procedures that could easily affect analgesic efficacy. Length of procedures also is a variable that could easily affect measures of analgesia and akinesia.
- H. **Skill of Anesthesiologist:** With local anesthesia, location of the injected anesthetic solution relative to the nerves being blocked could have a clear effect on overall efficacy as well as time to onset of anesthesia.
- I. **Sample Sizes:** Many of the interpretable studies are small, with sample sizes ranging from 27 to 150 patients. Numerical differences that are not statistically significant in small studies could become so with larger sample sizes.
- J. **Potential Bias:** While most of the studies were double-blind, three were randomized but open, one positive(30), and two negative(37,39) allowing potential bias.

The variability in study design, anesthetic agents utilized, hyaluronidase preparation utilized and endpoints is too large to allow for statistically meaningful interpretation of efficacy seen in these studies. With such variability, techniques such as meta-analysis cannot be applied.

The efficacy and dosing of Wydase® as an adjunct for ophthalmic anesthesia has been established in over 50 years of clinical use and confirmed by the DESI program review(18). Baxter believes that much of the inconsistency in efficacy results in the published literature is due to the previously noted confounding variables. Thus, it is possible for a new hyaluronidase product to demonstrate efficacy only through well designed, adequately powered clinical trials using a validated, clinically meaningful endpoint.

III. **Dosing Regimen:** The published literature does not provide a basis for selection of an appropriate dosing regimen for the use of a new hyaluronidase product in ophthalmic anesthesia. A review of the 88 published reports of clinical trials of hyaluronidase use in ophthalmologic anesthesia shows no consensus as to the dose of hyaluronidase that should be added to the anesthetic(s). Doses used in published studies for ophthalmologic anesthesia range from 3.75 IU/mL to 300 IU/mL. For the 16 studies interpretable for efficacy in this indication, the nine positive studies and seven negative studies used doses ranging from 7.5-150 IU/mL. The lack of any dose response in published controlled studies does not allow a new product to reference them for dosing information for labeling.

While pharmacokinetics might be used to show dose equivalence for two intravenous products, there is no equivalent bioassay for local tissue administration. With a biological product such as hyaluronidase, clinical dose ranging data are required to determine the optimal dose of a new product with a new source and new manufacturing process before that product can be approved for use as a spreading agent for other coadministered drugs.

Thus, approval of any new hyaluronidase product requires that the new product demonstrate the dosing, safety and efficacy that would be specific for that product and that method of administration, data that would need to be generated with adequately designed and sized clinical trials or by demonstrating that the new product is analytically identical to Wydase® and has the same pharmacokinetic and pharmacodynamic characteristics as Wydase® in local tissue applications.

C. *Environmental Impact.*

The Petitioner claims a categorical exclusion under 21 C.F.R. § 25.31(a) and (g).

D. *Economic Impact.*

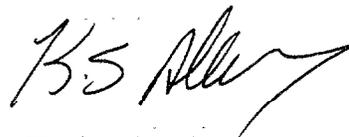
The petitioner will submit economic impact information upon request of the Commissioner.

E. *Certification*

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies and that it includes representative data and information known to the petitioner that are unfavorable to the petitioner.

Dated: October 24, 2003

Respectfully submitted,



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Attachments

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