IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF PENNSYLVANIA

ANITA HOCHENDONER; EARL HOCHENDONER; ANITA BOVA; JOSEPH M. CARIK; BARBARA J. CARIK; AMBER BRITTON; SHAWN BRITTON; CHERYL BRITTON; THOMAS OLSZEWSKI; DARLENE COOKINGHAM; and DAVID ROBERTS, Individually and on behalf of all others similarly situated,	)	Civil Action No.
Plaintiffs,	)	JURY TRIAL DEMANDED
v.	)	
GENZYME CORPORATION; and MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK,	)	
Defendants.	)	

COMPLAINT IN CIVIL ACTION

AND NOW come Plaintiffs Anita Hochendoner, Earl Hochendoner, Anita Bova, Joseph M. Carik, Barbara J. Carik, Amber Britton, Shawn Britton, Cheryl Britton, Thomas Olszewski, Darlene Cookingham, and David Roberts, individually and on behalf of others similarly situated, by and through their attorneys, Kurzweg Law Offices, C. Allen Black, Esq. and Matthew L. Kurzweg, Esq., and file this Complaint in Civil Action. In support thereof, Plaintiffs aver as follows:

PARTIES

1. Plaintiff Anita Hochendoner is an adult individual who currently resides in Pittsburgh, PA.

2. Plaintiff Earl Hochendoner is an adult individual who currently resides Pittsburgh, PA and is the

spouse of Anita Hochendoner.

3. Plaintiff Anita Bova is an adult individual who currently resides in Pittsburgh, PA.
4. Plaintiff Joseph M. Carik is an adult individual who currently resides in North Las Vegas, NV.
5. Plaintiff Barbara J. Carik is an adult individual who currently resides in Pittsburgh, PA and is the spouse of Joseph M. Carik.
6. Plaintiff Amber Britton is an adult individual who currently resides in Kirkland, WA.
7. Plaintiff Shawn Britton is an adult individual who currently resides in Seattle, WA.
8. Plaintiff Cheryl Britton is an adult individual who currently resides Seattle, WA and is the spouse of Shawn Britton.
9. Plaintiff Thomas Olszewski is an adult individual who currently resides in Grayling, MI.
10. Plaintiff Darlene Cookingham is an adult individual who currently resides in Grayling, MI and is the spouse of Tom Olzewski.
11. Plaintiff David Roberts is an adult individual who currently resides in Goldsboro, NC.
12. Defendant Genzyme Corporation ("Genzyme") is a corporation organized and existing under the laws of the State of Massachusetts, with its headquarters and principal place of business located at 500 Kendall Street, Cambridge, MA 02142, and doing business within the Western District of Pennsylvania and elsewhere in the United States.
13. Defendant Mount Sinai School of Medicine of the City University of New York ("Mt. Sinai") is a corporation organized and existing under the laws of the State of New York, with its headquarters and principal place of business located at One Gustave L. Levy Place, New York, NY 10029-6574. Mt. Sinai holds limited title to and is the sole licensor of U.S. Patent No. 5,356,804 to

Genzyme for the manufacture of Fabrazyme®.

JURISDICTION AND VENUE

14. Jurisdiction is conferred upon this judicial district pursuant to federal question jurisdiction under 28 U.S.C. §1331. This Court also has diversity jurisdiction pursuant to 28 U.S.C. § 1332(a) (1) because the Plaintiffs are citizens of a State different from one or more Defendants and the aggregate amount in controversy exceeds seventy five thousand ($75,000), exclusive of interest and costs. Jurisdiction is further conferred under 28 U.S.C. §§ 1331 and 1337. This Court also has diversity jurisdiction over the Classes (as hereinafter defined) pursuant to 28 U.S.C. §§ 1332(d) (2) and (6) of the Class Action Fairness Act of 2005 because one or more members of the Classes are citizens of a State different from one or more Defendants and the aggregate amount in controversy exceeds five million dollars ($5,000,000), exclusive of interest and costs.

15. Venue is proper in the Western District of Pennsylvania pursuant to 28 U.S.C. § 1391(a)(2) and(b)(2) because Defendants transact business within this district either by direct sale or underlying license agreements with three of the Plaintiffs, and injury to these three or more of the Plaintiffs occurred in this district.

16. Additional out-of-state Plaintiffs join the instant case under the Federal Rules of Civil Procedure Rule 20(a)(1)(A) and (B) as all injuries arose from a common fact and present a common question of law.

FACTUAL BACKGROUND

17. Plaintiffs Anita Hochendoner, Anita Bova, Joseph M. Carik, Amber Britton, Shawn Britton, Tom Olszewski, and David Roberts suffer from Fabry Disease, which is heritable genetic illness and

results in the body being unable to synthesize the enzyme alpha-galactosidase A, which is critical for the degradation and export of fats from cells.

18. Fabry disease is a life-threatening illness and without treatment results in the premature death of Fabry patients from complications such as renal disease, heart attack, and stroke.

19. Left untreated, Branton *et al.*, "Natural History and Treatment of Renal Involvement in Fabry Disease;" J. Am. Soc. Nephrol. 13:S139-S143 (2002) found from survival analysis that 50% of patients developed End Stage Renal Disease "ESRD" by 53 years, with a range of 21 to 56 years. Importantly, all patients in this National Institute of Health ("NIH") study who lived into their 50s developed ESRD.

20. While no cure for Fabry is yet available, one of the greatest breakthroughs in scientific research on Fabry disease has been the discovery that enzyme replacement therapy with agalsidase beta (Fabrazyme®) can effectively treat Fabry patients.

21. The scientific research on Fabry disease that led to the breakthrough was a direct result of taxpayer funding.

22. Specifically, the NIH awarded grant no. DK 34045 to Dr. Robert J. Desnick at the Mount Sinai School of Medicine of New York University to develop Fabrazyme® as an enzyme replacement therapy to treat Fabry Disease.

23. Mt. Sinai was granted U.S. Patent No. 5,356,804 to a method of producing agalsidase beta subject to the requirements and obligations of 35 U.S.C. §§ 200-212, commonly known as the Bayh-Dole Act.

24. Mt. Sinai exclusively licensed U.S. Patent No. 5,356,804 for the manufacture of agalsidase beta

(Fabrazyme®) to Genzyme Corporation, which is the sole supplier of the drug to the U.S. marketplace.

25. In April 2003, the Food and Drug Administration "FDA" granted approval for Genzyme to market Fabrazyme® for treatment of Fabry patients.

26. The FDA approval of Fabrazyme® was based on a recommended prescribed dose of 1 mg/kg body weight infused every two weeks as an intravenous (IV) infusion. See FDA approved package insert, attached hereto and incorporated herein as Exhibit A.

27. No other enzyme replacement therapy is approved in the U.S., although a slightly different molecule, designated agalsidase-alfa (Replagal®) is marketed overseas for treatment of Fabry disease.

28. From the date of approval until approximately June 2009, Genzyme was able to manufacture enough Fabrazyme® to treat all currently diagnosed Fabry patients in the U.S.

29. However, sometime before June 2009, Genzyme decreased production of Fabrazyme® as a result of a viral infection in their Allston Landing, MA manufacturing plant.

30. Genzyme caused the viral infection of Fabrazyme® by failing to clean and sterilize their bioreactors between production batches, and thus introduced the virus by cross-contamination.

31. Specifically, Genzyme would use the same bioreactors to produce both Fabrazyme® and a different biological drug, Cerezyme®, which is used to treat another enzyme deficiency termed Gaucher disease.

32. The Cerezyme® production batches were initially contaminated with the non-human Vesivirus 2117.

33. Genzyme then cross-contaminated Fabrazyme® cultures by failing to properly clean and sterilize the bioreactors before switching it for Fabrazyme® production

34. The Allston Landing facility was the subject of a FDA warning letter that followed an inspection in September and October of 2008. One of the FDA's concerns was controls to protect against microbial contamination,

35. Further, in November 2009, Genzyme produced Fabrazyme® vials that contained contaminants of particulate steel, glass and rubber.

36. The FDA initiated action against Genzyme which resulted in a consent decree in May 2010, which included a $175 million dollar fine and oversight of the manufacture of Fabrazyme® for at least 7 years.

37. In June 2009, as a direct result of its reduced production of Fabrazyme®, Genzyme unilaterally implemented a rationing plan for its reduced supply of Fabrazyme® for the then known Fabry patients, wherein Genzyme unilaterally limited then known Fabry patients to receiving only less than one-third (1/3) of the recommended prescribed dose ("Genzyme Rationing Plan").

38. By and through the Genzyme Rationing Plan, Genzyme also unilaterally barred any newly diagnosed patients from receiving Fabrazyme®.

39. Until about June 2009, Plaintiffs Joseph M. Carik, Anita Hochendoner, Anita Bova, David Roberts, and Tom Olszewski, and all other then known Fabry patients similarly situated, were receiving the recommended prescribed dose, but after June 2009, Genzyme reduced their respective doses to less than one-third of the FDA approved dose pursuant to the Genzyme Rationing Plan.

40. On or about January 2010, pursuant to the Genzyme Rationing Plan, Genzyme slightly increased doses to only 50% of the recommended prescribed dose to Plaintiffs Joseph M. Carik, Anita Hochendoner, Anita Bova, David Roberts and Tom Olszewski, and all other then known Fabry patients similarly situated.

41. As of this filing, almost two years after the Genzyme Rationing Plan began, Plaintiffs Joseph M. Carik, Anita Hochendoner, Anita Bova, David Roberts and Tom Olszewski as well as all other Fabry patients similarly situated in the United States being treated with Fabrazyme® do not receive the FDA approved dose from Genzyme as a direct result of the Genzyme Rationing Plan.

42. Plaintiffs Amber Britton and Shawn Britton were diagnosed with Fabry disease after June 2009.

43. Under the Genzyme Rationing Plan, after June of 2009, Genzyme barred all newly diagnosed Fabry patients from receiving any Fabrazyme®.

44. Under the Genzyme Rationing Plan, Genzyme barred Plaintiffs Amber Britton and Shawn Britton and all other Fabry patient similarly situated from receiving Fabrazyme®, despite immediate treatment with Fabrazyme® being medically indicated.

45. As of this filing, almost two years after the Genzyme Rationing Plan began, Genzyme still bars Fabrazyme® access to Plaintiffs Amber Britton and Shawn Britton and other United States citizens similarly situated and diagnosed with Fabry disease after June 2009.

46. Defendant Mt. Sinai knew of the Genzyme Rationing Plan, and despite having statutory duties to the contrary described hereinafter, with knowledge, consented to the Genzyme Rationing Plan under its exclusive license agreement with Genzyme.

47. Genzyme was aware of adverse events and/or the potential for such adverse events by reducing the

dose of Fabrazyme® below FDA approved levels.

48. Similarly, Mt. Sinai was also aware of adverse events and/or the potential for such adverse events associated with Genzyme's Rationing Plan, but consented and/or maintained consent for licensing the patent for Fabrazyme® despite having a duty to protect against the invention's unreasonable use and non-use under the Bayh-Dole Act.

49. Mt. Sinai was also aware that that Genzyme banned newly diagnosed patients from receiving Fabrazyme® and consented to Genzyme's banning the drug to new patients despite having a duty to protect against the invention's unreasonable use and non-use under the Bayh-Dole Act.

50. Mt. Sinai never informed the NIH of the Genzyme Rationing Plan and the resultant unreasonable use and non-use of the invention that was secured under the Bayh-Dole act, thereby concealing the violations of the Bayh-Dole act from the NIH.

51. Neither Mt. Sinai nor Genzyme has ever applied for regulatory approval of the Genzyme Rationing Plan or administration of a reduced Fabrazyme® dose to treat Fabry disease.

52. Neither Mt. Sinai nor Genzyme has ever shown that a reduced dose of Fabrazyme® is either safe or efficacious for treating Fabry disease.

53. Neither Mt. Sinai nor Genzyme has ever informed patients as to what adverse events have been observed or could result from the Genzyme Rationing Plan.

54. On October 22, 2010, the European Medical Agency ("EMA") issued a press release stating that "The [European Medicines Agency's Committee for Medicinal Products for Human Use] CHMP is now recommending that physicians switch back to prescribing the full dose of Fabrazyme

according to the authorised product information, depending on the availability of enzyme replacement therapy and the severity of the disease." See EMA recommendation for full dosage of Fabrazyme® for Fabry Patients, attached hereto and incorporated herein as Exhibit B.

55. The EMA's recommendation was based on the observation "that since the introduction of a lower dose of Fabrazyme in June 2009, there has been a steady increase in the number of reported adverse events, matching the increase in the number of patients on the lower dose. At first, most of the events were pain-related, soon followed by reports of events affecting the heart, the central nervous system and the kidneys." Id.

56. On November 16, 2010, the EMA publicly published a statistical study on the Fabrazyme supply shortage in Europe, which showed that patients not only had a return of life threatening symptoms but also an accelerated course of deterioration on the lowered dose. See EMA study attached hereto and incorporated herein as Exhibit C.

57. The EMA found that "In the early stages of the shortage the main increases in AEs [adverse events] were related to pain/paresthesia events, while later on in the shortage period, the main increases were in serious cardiac events such as myocardial infarction, in serious nervous disorders such as stroke, and – possibly to a lesser extent – in renal disorders. There have been consistent reports of a higher percentage of patients reporting peripheral pain, abdominal pain and diarrhoea on a daily basis after 25 June 2009 (start of the shortage)." Id.

58. Genzyme participated in the EMA study as part of its administration of the "Fabry Registry," a database collecting information on all Fabry patients, and Genzyme was aware of the EMA's results.

59. Genzyme did not and has not informed its patients of the results of the EMA study.

60. In August of 2010, Plaintiffs Joseph Carik, Anita Hochendoner, Anita Bova and Amber Britton requested that the NIH exercise its march-in rights under the Bayh-Dole Act to allow other manufacturers to enter the market to make Fabrazyme® under U.S. Patent No. 5,356,804.

61. On December 1, 2010, the NIH denied the petitioners' request stating that the three-year approval process for new manufacturers under FDA regulations render the Bayh-Dole remedy of march-in useless for alleviating drug shortages in a timely manner, despite the NIH recognition of the critical health need of patients for the drug.

62. As a direct result of the Genzyme Rationing Plan and/or Genzyme's denial of access to drug and/or sale of adulterated drug, Fabry patients have either had a return of symptoms, accelerated disease development, injury, and otherwise preventable disease progression, or have died during the shortage.

CLASS ALLEGATIONS

63. Paragraphs 1 through 62 are incorporated hereunder as though fully set forth at length.

64. Plaintiffs are bringing this action on behalf of themselves and all others similarly situated, which includes any and all individuals residing in the United States who have been diagnosed with Fabry disease, and their spouses ("Classes").

65. The proposed Classes are so numerous that joinder of all members of the Classes is impractical and the administration of the claims as set forth herein on behalf of the Classes is more efficient and will benefit the parties and the Court.

66. The questions of law and fact common to the Classes predominate over the questions affecting

only individual members of the Classes.

67. Plaintiffs' claims as set forth herein are typical of the claims of the Classes, as they have all suffered a similar harm as a result of the Defendants' actions and omissions.

68. Plaintiffs will fairly and adequately represent and protect the interests of the members of the Classes because their interests do not conflict with the interests of the individual members of the Classes. Plaintiffs have retained competent and experienced counsel to represent themselves and the members of the Classes.

69. Adjudication of the claims set forth herein as a class action is superior to individual litigation of the claims, which would be impractical, expensive, and unduly burdensome to the Court.

COUNT I: NEGLIGENCE

ANITA HOCHENDONER, ANITA BOVA, JOSEPH M. CARIK, DAVID ROBERTS, TOM OLSZEWSKI, AMBER BRITTON, AND SHAWN BRITTON, INDIVIDUALLY AND ON BEHALF OF ALL OTHER SIIMILARLY SITUATED v. GENZYME CORPORATION AND MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK

70. Paragraphs 1 through 69 are incorporated hereunder as though fully set forth at length.

71. The injuries sustained by Plaintiffs were due to and were the direct and proximate result of the negligence, carelessness, and recklessness of Defendants Genzyme and Mt. Sinai generally, and under the following particulars:

a. in that Defendants failed to take reasonable steps to avoid and prevent viral contamination in the Genzyme Allston Landing, MA plant;
b. in that Defendants failed to take reasonable steps to avoid and prevent contamination of Fabrazyme® vials with particulate steel, glass and rubber;
c. in that the Defendants unilaterally devised, implemented, and/or approved with knowledge and consent the Genzyme Rationing Plan, and/or otherwise reduced or consented to reducing the dose of Fabrazyme® or denied it entirely for treatment of Fabry patients;

d. in that Defendants sold Fabrazyme® vials contaminated with glass, rubber and steel particles;

e. in that the Defendants designed and implemented and/or consented to the Genzyme Rationing Plan despite a statutory duty to ensure that Fabrazyme® was made available to all U.S. citizens and at the required dose pursuant to the Bayh-Dole Act's prohibition against non-use or unreasonable use of publically funded inventions under 35 U.S.C §200, specifically U.S. Patent No. 5,356,804;

f. in that the Defendants instructed and/or through knowledge and consent reduced the dose of Fabrazyme® to dangerous, sub-efficacious and unapproved levels;

g. in that the Defendants failed to test or require the testing of the effects of reducing the dosage of Fabrazyme® to unapproved levels to treat Fabry disease;

h. in that the Defendants failed to provide adequate warnings and/or cautions and/or directions concerning the dangers and limitations of the reduced dosage of Fabrazyme;

i. in that the Defendants failed to provide or require proper and/or adequate reserves of unadulterated Fabrazyme® in order to prevent or mitigate manufacturing errors;

j. in that the Defendants failed to provide or license a second source of manufacture for Fabrazyme® in order to prevent or mitigate life-threatening supply chain disruptions; and

k. in otherwise failing to exercise the care and caution that a reasonable, careful and prudent entity would have or should have exercised under the circumstances.

72. As a direct and proximate result of the negligence of Defendants, the Plaintiffs have sustained the following serious injuries, some or all which may be of a permanent nature:

a. renal injury;

b. cardiac injury;

c. neurological injury;

d. peripheral pain;

e. chronic abdominal pain and diarrhea;

f. impairment of vision;

g. impairment of hearing; and

h. premature death and other serious and permanent injuries.

73. As a direct and proximate result of the aforesaid injuries, Plaintiffs have been damaged as follows:

a. Plaintiffs have been and will be required to expend large sums of money for medical and surgical attention, medical and surgical supplies, medical and surgical appliances, and medicines;

b. Plaintiffs have suffered and will continue to suffer great pain, suffering, inconvenience, impairment of bodily function, and mental anguish;

c. Plaintiffs have been and will be deprived of earnings and earning capacity;

d. Plaintiffs have suffered loss of enjoyment of life;

e. Plaintiffs have died or suffered a reduced life expectancy; and

f. Plaintiffs' general health, strength and vitality have been impaired.

WHEREFORE, Plaintiffs Anita Hochendoner, Anita Bova, Joseph M. Carik, David Roberts, Tom Olszewski, Amber Britton, and Shawn Britton, individually and on behalf of all others similarly situated, demand judgment against Defendants, Genzyme Corporation and Mount Sinai School of Medicine of the City University of New York, jointly and severally in an amount in excess of $75,000.00, together with costs of suit. JURY TRIAL DEMANDED.

COUNT II: NEGLIGENCE *Per Se*

ANITA HOCHENDONER, ANITA BOVA, JOSEPH M. CARIK, DAVID ROBERTS, TOM OLSZEWSKI, AMBER BRITTON, AND SHAWN BRITTON, INDIVIDUALLY AND ON BEHALF OF ALL OTHER SIIMILARLY SITUATED v. GENZYME CORPORATION AND MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK

74. Paragraphs 1 through 73 are incorporated hereunder as though fully set forth at length.

75. Defendants Genzyme and Mt. Sinai are strictly liable to Plaintiffs as follows under the Food, Drug, and Cosmetics Act 21 USC §351(a-d) regarding adulterated products, 21 USC §352(f) regarding adequate warning and labeling, 21 USC §355(j) regarding the statutory approval process for testing of previously unapproved doses, and 21 USC §356a(a) regarding testing required for substantial manufacturing changes; as well as being strictly liable under the Bayh-Dole Act 35 USC

§200 regarding the prohibition of unreasonable use or non-use of Bayh-Dole regulated inventions which are necessary for human health:

a. for restricting and/or consenting to restriction of administering Fabrazyme® at a dose that is below the FDA approved use of 1 mg/kg body weight infused every two weeks;
b. for failing to seek FDA approval for using the reduced dosage to treat Fabry disease;
c. for selling Fabrazyme® contaminated with glass, rubber and steel particles;
d. for failure to give adequate and complete warnings of the known or knowable dangers involved in the use Fabrazyme® at a reduced dose as required by FDA regulations;
e. for unreasonably using a publicly funded invention by restricting administration to below the FDA approved dose and for non-use of the invention by banning the publicly funded invention from being given to newly diagnosed Fabry patients;
f. for failing to provide or require proper and/or adequate reserves of unadulterated Fabrazyme® in order to prevent or mitigate manufacturing errors;
g. for failing to provide or license a second source of manufacture for Fabrazyme® in order to prevent or mitigate life-threatening supply chain disruptions; and
h. in otherwise failing to exercise the care and caution that a reasonable, careful and prudent entity would have or should have exercised under the circumstances.

76. By virtue of the negligence *per se* of Defendants, Defendants are liable for the severe injuries and conditions as set forth herein of Plaintiffs Anita Hochendoner, Anita Bova, Joseph M. Carik, David Roberts, Thomas Olszewski, Amber Britton, Shawn Britton, and all others similarly situated.

77. As a direct and proximate result of the aforesaid injuries, Plaintiffs Anita Hochendoner, Anita Bova, Joseph M. Carik, David Roberts, Tom Olszewski, Amber Britton, Shawn Britton, and all others similarly situated have suffered damages as set forth herein.

WHEREFORE, Plaintiffs Anita Hochendoner, Anita Bova, Joseph M. Carik, David Roberts, Tom Olszewski, Amber Britton, Shawn Britton, individually and on behalf of all others similarly situated, demand judgment against Defendants Genzyme Corporation and Mount Sinai School of Medicine of the

City University of New York, jointly and severally in an amount in excess of $75,000.00, together with costs of suit. JURY TRIAL DEMANDED.

COUNT III: STRICT LIABILITY

ANITA HOCHENDONER, ANITA BOVA, JOSEPH M. CARIK, DAVID ROBERTS, TOM OLSZEWSKI, AMBER BRITTON, AND SHAWN BRITTON, INDIVIDUALLY AND ON BEHALF OF ALL OTHER SIIMILARLY SITUATED v. GENZYME CORPORATION AND MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK

78. Paragraphs 1 through 77 are incorporated hereunder as though fully set forth at length.

79. Defendants Genzyme and Mt. Sinai are strictly liable to Plaintiffs as follows:

    a. for failure to adequately and safely label the reduced dosage of Fabrazyme®;
    b. for selling and/or licensing the use of Fabrazyme® at a defective dose;
    c. for selling Fabrazyme® in a defective condition being adulterated with glass, rubber and steel particles;
    d. for selling and/or licensing the use of Fabrazyme® at a reduced dose when the dose is untested and unreasonably dangerous for its intended use; and
    e. for failure to give adequate and complete warnings of the known or knowable dangers involved in the use Fabrazyme® at a reduced dose.

80. By virtue of the strict liability of Defendants, Defendants are liable for the severe injuries and conditions as set forth herein of Plaintiffs Anita Hochendoner, Anita Bova, Joseph M. Carik, David Roberts, Thomas Olszewski, Amber Britton, Shawn Britton, and all others similarly situated.

81. As a direct and proximate result of the aforesaid injuries, Plaintiffs Anita Hochendoner, Anita Bova, Joseph M. Carik, David Roberts, Tom Olszewski, Amber Britton, Shawn Britton, and all others similarly situated have suffered damages as set forth herein.

WHEREFORE, Plaintiffs Anita Hochendoner, Anita Bova, Joseph M. Carik, David Roberts, Tom Olszewski, Amber Britton, Shawn Britton, individually and on behalf of all others similarly situated,

demand judgment against Defendants Genzyme Corporation and Mount Sinai School of Medicine of the City University of New York, jointly and severally in an amount in excess of $75,000.00, together with costs of suit. JURY TRIAL DEMANDED.

COUNT IV: BREACH OF WARRANTY

ANITA HOCHENDONER, ANITA BOVA, JOSEPH M. CARIK, DAVID ROBERTS, TOM OLSZEWSKI, AMBER BRITTON, AND SHAWN BRITTON, INDIVIDUALLY AND ON BEHALF OF ALL OTHER SIIMILARLY SITUATED v. GENZYME CORPORATION AND MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK

82. Paragraphs 1 through 81 are incorporated hereunder as though fully set forth at length.

83. All of the resultant losses, damages and injuries sustained by Plaintiffs resulted directly and proximately from Defendants Genzyme's and Mt. Sinai's breach of express and/or implied warranties of merchantability or fitness for the use of Fabrazyme®, in the following particulars:

a. the Defendants failed to adequately, properly, and/or timely test the reduced dose prior to use;
b. Fabrazyme®, given at reduced dosage and/or being adulterated with glass, steel, and rubber particles, is not fit for the ordinary purpose for which it is customarily or foreseeably used;
c. the Defendants knew or should have known that the adulterated drug and/or reduced dosage of Fabrazyme® is dangerous and likely to cause damage to users;
d. Fabrazyme®, given at reduced dosage and/or being adulterated, was not of merchantable quality and was not in conformity, insofar as safety is concerned, with products used in a normal course of business and/or statutory mandates;
e. the Defendants knew or should have known that in order to make Fabrazyme® effective for its intended use, they should have provided the drug at the recommended dose;
f. the Defendants knew or should have known, that due to the inherently dangerous nature of the design of the dosing schedule and/or the drug adulteration, they should have provided warnings on the product to protect users;
g. the Defendants did not keep abreast of the state of the art in the science and/or knew of adverse events involving reduced dosage and failed to warn users;
h. the Defendants did not disclose to the users of the reduced dosage of Fabrazyme® that the

dosing was defectively and/or unreasonably designed, thereby making the product dangerous to use;

i. the Defendants knew or should have known that users were relying upon the expertise of the Defendants in designing, fabricating, manufacture, labeling and/or supplying Fabrazyme®;

j. in expressly or impliedly warranting that Fabrazyme® was in accordance with statutory mandates and efficacious; and/or

k. in expressly or impliedly misrepresenting that the reduced dose of Fabrazyme® was in accordance with statutory mandates and efficacious for use.

84. As a direct and proximate cause of the breach of these expressed or implied warranties, Plaintiffs Anita Hochendoner, Anita Bova, Joseph M. Carik, David Roberts, Thomas Olszewski, Amber Britton, Shawn Britton, and all others similarly situated suffered severe injuries and/or conditions as set forth herein.

85. As a result of their injuries and conditions, Plaintiffs Anita Hochendoner, Anita Bova, Joseph M. Carik, David Roberts, Thomas Olszewski, Amber Britton, Shawn Britton, and all others similarly situated have suffered damages as set forth herein.

WHEREFORE, Plaintiffs Anita Hochendoner, Anita Bova, Joseph M. Carik, David Roberts, Tom Olszewski, Amber Britton, Shawn Britton, individually and on behalf of all others similarly situated, demand judgment against Defendants Genzyme Corporation and Mount Sinai School of Medicine of the City University of New York, jointly and severally in an amount in excess of $75,000.00, together with costs of suit. JURY TRIAL DEMANDED.

COUNT V: VIOLATION OF BAYH-DOLE ACT PROSCRIPTION OF NON-USE OR UNREASONABLE USE OF PUBLICALLY FUNDED INVENTIONS (IMPLIED CAUSE OF ACTION)

ANITA HOCHENDONER, ANITA BOVA, JOSEPH M. CARIK, DAVID ROBERTS, TOM OLSZEWSKI, AMBER BRITTON, AND SHAWN BRITTON, INDIVIDUALLY AND ON BEHALF OF ALL OTHER SIIMILARLY SITUATED v. GENZYME CORPORATION AND MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK

86. Paragraphs 1 through 85 are incorporated hereunder as though fully set forth at length.

87. The injuries sustained by Plaintiffs were due to Defendants Genzyme and Mt. Sinai violating the Bayh-Dole Act 35 U.S.C. §200, generally and under the following particulars:

a. in that the Defendants reduced the dose of Fabrazyme® or denied it entirely for Plaintiffs' Fabry disease thereby unreasonably using or/and not using the publicly-funded invention, U.S. Patent No. 5,356,804;

b. in that the Defendants instituted the drug ban for some citizens and rationing to other citizens despite a statutory duty to ensure that Fabrazyme® was made available to U.S. citizens and at the required dose pursuant to the Bayh-Dole Act's specific prohibition against a contractor's non-use and unreasonable use of publically funded invention under 35 U.S.C. §200;

c. in that the Defendants failed to require or provide adequate safeguards to prevent or mitigate damages resulting from the unreasonable use and non-use of publicly-funded invention, U.S. Patent No. 5,356,804;

d. in that the Defendants instituted the rationing and denial of access despite lacking title or other property right to any patent right of non-use or unreasonable use that otherwise may be allowed under 35 U.S.C. § 271(d)(4); and

in that the Defendants caused special injuries unique to the class arising out of the non-use and unreasonable use of the invention because the Plaintiffs have Fabry disease and rely on access to the publicly funded invention, Fabrazyme®, specifically to treat their disease, which is otherwise fatal.

88. By virtue of the violation of the Bayh-Dole Act, Defendants are liable for the severe injuries and conditions of Plaintiffs Anita Hochendoner, Anita Bova, Joseph M. Carik, David Roberts, Thomas Olszewski, Amber Britton, Shawn Britton, and all others similarly situated as set forth herein.

89. As a result of their injuries and conditions, Plaintiffs Anita Hochendoner, Anita Bova, Joseph M. Carik, David Roberts, Thomas Olszewski, Amber Britton, Shawn Britton, and all others similarly

situated have suffered damages as set forth herein.

WHEREFORE, Plaintiffs Anita Hochendoner, Anita Bova, Joseph M. Carik, David Roberts, Tom Olszewski, Amber Britton, Shawn Britton, individually and on behalf of all others similarly situated, demand judgment against Defendants Genzyme Corporation and Mount Sinai School of Medicine of the City University of New York, jointly and severally in an amount in excess of $75,000.00, together with costs of suit. JURY TRIAL DEMANDED.

COUNT VI: PENNSYLVANIA STATE LAW DECEPTIVE TRADE PRACTICE VIOLATION (73 P.S. §§201-1 - 201-9.2)

ANITA HOCHENDONER AND ANITA BOVA, INDIVIDUALLY AND ON BEHALF OF ALL OTHERS SIMILARLY SITUATED v. GENZYME CORPORATION AND MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK

90. Paragraphs 1 through 89 are incorporated hereunder as though fully set forth at length.

91. All of the resultant losses, damages and injuries sustained by Plaintiffs resulted directly and proximately from Defendants Genzyme's and Mt. Sinai's deceptive acts or practices regarding the sale and use of Fabrazyme®, generally, and in the following particulars:

    a. failing to inform the Plaintiffs that the dosage given was below the certified and approved FDA use and/or the possible consequences of such unapproved use;
    b. affirmatively representing that the drug given at reduced dosage and/or contaminated with glass, rubber and steel particles is approved to successfully treat Fabry disease and/or Fabry disease patients will benefit from such use; and
    c. in expressly or impliedly misrepresenting that the reduced dose and/or adulterated Fabrazyme® was in accordance with statutory mandates and/or efficacious for use.

92. By the use of deceptive trade practices, Defendants are liable for the severe injuries and conditions of Plaintiffs Anita Hochendoner and Anita Bova, and all others similarly situated, as set forth

herein.

93. As a direct and proximate result of the aforesaid injuries, Anita Hochendoner and Anita Bova, and all others similarly situated, have suffered damages as set forth herein.

WHEREFORE, Plaintiffs Anita Hochendoner and Anita Bova, individually and on behalf of all others similarly situated, demand judgment against Defendants Genzyme Corporation and Mount Sinai School of Medicine of the City University of New York, jointly and severally in an amount in excess of $75,000.00, together with treble damages and costs of suit. JURY TRIAL DEMANDED.

COUNT VII: NEVADA STATE LAW DECEPTIVE TRADE PRACTICE VIOLATION (NEVADA REVISED STATUTES §§ 598.0903-0990)

JOSEPH M. CARIK INDIVIDUALLY AND ON BEHALF OF ALL OTHERS SIMILARLY SITUATED v. GENZYME CORPORATION AND MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK

94. Paragraphs 1 through 93 are incorporated hereunder as though fully set forth at length.

95. All of the resultant losses, damages and injuries sustained by Plaintiff resulted directly and proximately from Defendants Genzyme's and Mt. Sinai's deceptive acts or practices regarding the sale and use of the drug, Fabrazyme®, generally, and in the following particulars:

    a. failing to inform the Plaintiff that the dosage given was below the certified and approved FDA use and/or the possible consequences of such unapproved use;
    b. affirmatively representing that the drug given at reduced dosage and/or contaminated with glass, rubber and steel particles is approved to successfully treat Fabry disease and/or Fabry disease patients will benefit from such use; and
    c. in expressly or impliedly misrepresenting that the reduced dose and/or adulterated Fabrazyme® was in accordance with statutory mandates and/or efficacious for use.

96. By the use of deceptive trade practices, Defendants are liable for the severe injuries and conditions of Plaintiff Joseph M. Carik, and all others similarly situated, as set forth herein.

97. As a direct and proximate result of the aforesaid injuries, Joseph M. Carik, and all others similarly situated, have suffered damages as set forth herein.

WHEREFORE, Plaintiff Joseph M. Carik demands judgment against Defendants Genzyme Corporation and Mount Sinai School of Medicine of the City University of New York, jointly and severally in an amount in excess of $75,000.00, together with punitive damages, and costs of suit. JURY TRIAL DEMANDED.

COUNT VIII: MICHIGAN STATE LAW DECEPTIVE TRADE PRACTICE VIOLATION (MICHIGAN COMPILED LAWS § 445.903 *et seq.)*

THOMAS OLSZEWSKI, INDIVIDUALLY AND ON BEHALF OF ALL OTHERS SIMILARLY SITUATED v. GENZYME CORPORATION AND MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK

98. Paragraphs 1 through 97 are incorporated hereunder as though fully set forth at length.

99. All of the resultant losses, damages and injuries sustained by Plaintiff resulted directly and proximately from Defendants Genzyme's and Mt. Sinai's deceptive acts or practices regarding the sale and use of the drug, Fabrazyme®, generally, and in the following particulars:

a. failing to inform the Plaintiff that the dosage given was below the certified and approved FDA use and/or the possible consequences of such unapproved use;
b. affirmatively representing that the drug given at reduced dosage and/or contaminated with glass, rubber and steel particles is approved to successfully treat Fabry disease and/or Fabry disease patients will benefit from such use; and
c. in expressly or impliedly misrepresenting that the reduced dose and/or adulterated Fabrazyme® was in accordance with statutory mandates and/or efficacious for use.

100. By the use of deceptive trade practices, Defendants are liable for the severe injuries and conditions of Plaintiff Thomas Olzewski, and all others similarly situated, as set forth herein.

101. As a direct and proximate result of the aforesaid injuries, Thomas Olzewski, and all others similarly situated, have suffered damages as set forth herein.

WHEREFORE, Plaintiff Thomas Olszewski demands judgment against Defendants Genzyme Corporation and Mount Sinai School of Medicine of the City University of New York, jointly and severally in an amount in excess of $75,000.00, together with treble damages and costs of suit. JURY TRIAL DEMANDED.

COUNT IX: NORTH CAROLINA UNFAIR AND DECEPTIVE TRADE PRACTICES ACT VIOLATION (N.C. G.S. § 75-1.1 *et seq.*)

DAVID ROBERTS, INDIVIDUALLY AND ON BEHALF OF ALL OTHERS SIMILARLY SITUATED v. GENZYME CORPORATION AND MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK

102. Paragraphs 1 through 101 are incorporated hereunder as though fully set forth at length.

103. All of the resultant losses, damages and injuries sustained by Plaintiff resulted directly and proximately from Defendants Genzyme's and Mt. Sinai's deceptive acts or practices regarding the sale and use of the drug, Fabrazyme®, generally, and in the following particulars:

a. failing to inform the Plaintiff that the dosage given was below the certified and approved FDA use and/or the possible consequences of such unapproved use;
b. affirmatively representing that the drug given at reduced dosage and/or contaminated with glass, rubber and steel particles is approved to successfully treat Fabry disease and/or Fabry disease patients will benefit from such use; and
c. in expressly or impliedly misrepresenting that the reduced dose and/or adulterated Fabrazyme® was in accordance with statutory mandates and/or efficacious for use.

104. By the use of deceptive trade practices, Defendants are liable for the severe injuries and conditions of Plaintiff David Roberts, and all others similarly situated, as set forth herein.

105. As a direct and proximate result of the aforesaid injuries, David Roberts, and all others similarly situated, have suffered damages as set forth herein.

WHEREFORE, Plaintiff David Roberts demands judgment against Defendants Genzyme Corporation and Mount Sinai School of Medicine of the City University of New York, jointly and severally in an amount in excess of $75,000.00, together with treble damages and costs of suit. JURY TRIAL DEMANDED.

COUNT X: LOSS OF CONSORTIUM

BARBARA J. CARIK, EARL HOCHENDONER, CHERYL BRITTON, AND DARLENE COOKINGHAM, INDIVIDUALLY AND ON BEHALF OF ALL OTHERS SIMILARLY SITUATED v. GENZYME CORPORATION AND MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK

106. Paragraphs 1 through 105 of the Complaint are incorporated as if set forth fully at length herein.

107. As a direct and proximate result of the injuries sustained by their spouses, Plaintiffs have been damaged as follows:

a. Plaintiffs have been and will continue to be compelled to expend large sums of money for medical care, supplies, appliances, and medicine;
b. Plaintiffs have been and/or may be compelled to expend large sums of money for hiring help to perform household duties previously performed by their spouses; and
c. Plaintiffs have been and will be deprived of their spouse's aid, comfort, assistance, companionship, and consortium.

WHEREFORE, Plaintiffs Barbara J. Carik, Earl Hochendoner, Cheryl Britton, Darlene Cookingham, individually and on behalf of all others similarly situated, demands judgment against Defendants Genzyme Corporation and Mount Sinai School of Medicine of the City University of New

York, jointly and severally in an amount in excess of $75,000.00, together with treble damages and costs of suit. JURY TRIAL DEMANDED.

Respectfully submitted,

/s/ Matthew L. Kurzweg
Matthew L. Kurzweg, Esquire
Pa.I.D. 76462

/s/ C. Allen Black
C. Allen Black, Jr., Esquire
Pa.I.D. #202501

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Fabrazyme safely and effectively. See full prescribing information for Fabrazyme.

Fabrazyme (agalsidase beta)
Injection, powder, lyophilized for solution for intravenous use
Initial U.S. Approval: 2003

INDICATIONS AND USAGE

Fabrazyme is indicated for use in patients with Fabry disease. Fabrazyme reduces globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types (1).

DOSAGE AND ADMINISTRATION

1 mg/kg body weight given every two weeks as an IV infusion. Patients should receive antipyretics prior to infusion (2).

Fabrazyme®
agalsidase beta
For intravenous infusion

5031 (07/10)

FPO BARCODE

FPO BARCODE

DOSAGE FORMS AND STRENGTHS

- Lyophilized powder for reconstitution with Sterile Water for Injection, USP to yield 5 mg/mL (3).
- Available as 35 mg or 5 mg single-use vials (3).

CONTRAINDICATIONS

- None (4).

WARNINGS AND PRECAUTIONS

- Life-threatening anaphylactic and severe allergic reactions have been observed in some patients during Fabrazyme infusions. If severe allergic or anaphylactic reactions occur, immediately discontinue administration of Fabrazyme and provide necessary emergency treatment. Appropriate medical support measures should be readily available when Fabrazyme is administered because of the potential for severe infusion reactions (5.1).
- Infusion reactions occurred in approximately 50 to 55% of patients during Fabrazyme administration in clinical trials. Some reactions were severe. In patients experiencing infusion reactions, pretreatment with an antipyretic and antihistamine is recommended. If an infusion reaction occurs, decreasing the infusion rate, temporarily stopping the infusion, and/or administrating additional antipyretics, antihistamines, and/or steroids may ameliorate the symptoms (5.2).
- If severe infusion reactions occur, immediate discontinuation of the administration of Fabrazyme should be considered, and appropriate medical treatment should be initiated. Severe reactions are generally managed with administration of antihistamines, corticosteroids, IV fluids and/or oxygen as clinically indicated (5.2).
- Patients with advanced Fabry disease may have compromised cardiac function, which may predispose them to a higher risk of severe complications from infusion reactions, and these patients should be monitored closely during Fabrazyme administration (5.3).
- Re-administration of Fabrazyme to patients who have previously experienced severe or serious allergic reactions to Fabrazyme should be done only after careful consideration of the risks and benefits of continued treatment, and only under the direct supervision of qualified personnel and with appropriate medical support measures readily available (5.4).

ADVERSE REACTIONS

- The most common adverse reactions reported are infusion reactions. Serious and/or frequently occurring (≥ 5% incidence) related adverse reactions, including infusion reactions, consisted of one or more of the following: chills, fever, feeling hot or cold, dyspnea, nausea, flushing, headache, vomiting, paresthesia, fatigue, pruritus, pain in extremity, hypertension, chest pain, throat tightness, abdominal pain, dizziness, tachycardia, nasal congestion, diarrhea, edema peripheral, myalgia, back pain, pallor, bradycardia, urticaria, hypotension, face edema, rash, and somnolence (6).

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme at 1-800-745-4447 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- No drug interaction studies were performed (7).
- No *in vitro* metabolism studies were performed (7).

USE IN SPECIFIC POPULATIONS

- Pregnancy: Registry available (8.1).
- Nursing Mothers: Registry available (8.3).

See 17 for PATIENT COUNSELING INFORMATION

Revised: May/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Fabrazyme® (agalsidase beta) is indicated for use in patients with Fabry disease. Fabrazyme reduces globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dosage of Fabrazyme is 1 mg/kg body weight infused every two weeks as an intravenous (IV) infusion. Patients should receive antipyretics prior to infusion *[see Warnings and Precautions (5.2)]*.

The initial IV infusion rate should be no more than 0.25 mg/min (15 mg/hr). The infusion rate may be slowed in the event of infusion reactions. After patient tolerance to the infusion is well established, the infusion rate may be increased in increments of 0.05 to 0.08 mg/min (increments of 3 to 5 mg/hr) with each subsequent infusion. For patients weighing < 30 kg, the maximum infusion rate should remain at 0.25 mg/min (15 mg/hr). For patients weighing ≥ 30 kg, the administration duration should not be less than 1.5 hours (based on individual patient tolerability).

Patients who have had a positive skin test to Fabrazyme or who have tested positive for anti-Fabrazyme IgE may be successfully re-challenged with Fabrazyme. The initial re-challenge administration should be a low dose at a lower infusion rate, e.g., 1/2 the therapeutic dose (0.5 mg/kg) at 1/25 the initial standard recommended rate (0.01 mg/min). Once a patient tolerates the infusion, the dose may be increased to reach the approved dose of 1 mg/kg and the infusion rate may be increased by slowly titrating upwards (doubled every 30 minutes up to a maximum rate of 0.25 mg/min), as tolerated.

2.2 Instructions for Use

Fabrazyme does not contain any preservatives. Vials are for single use only. Discard any unused product.

Avoid shaking or agitating this product. Do not use filter needles during the preparation of the infusion.

Reconstitution and Dilution (using Aseptic Technique)

1. Allow Fabrazyme vials and diluent to reach room temperature prior to reconstitution (approximately 30 minutes). The number of 35 mg and 5 mg vials needed is based on the patient's body weight (kg) and the recommended dose of 1 mg/kg.

   Select a combination of 35 mg and 5 mg vials so that the total number of mg is equal to or greater than the patient's number of kg of body weight.
2. Reconstitute each 35 mg vial of Fabrazyme by slowly injecting 7.2 mL of Sterile Water for Injection, USP down the inside wall of each vial. Roll and tilt each vial gently. Each vial will yield a 5 mg/mL clear, colorless solution (total extractable amount per vial is 35 mg, 7 mL).

   Reconstitute each 5 mg vial of Fabrazyme by slowly injecting 1.1 mL of Sterile Water for Injection, USP down the inside wall of each vial. Roll and tilt each vial gently. Each vial will yield a 5 mg/mL clear, colorless solution (total extractable amount per vial is 5 mg, 1 mL).
3. Visually inspect the reconstituted vials for particulate matter and discoloration. Do not use the reconstituted solution if there is particulate matter or if it is discolored.
4. The reconstituted solution should be further diluted with 0.9% Sodium Chloride Injection, USP to a total volume based on patient weight specified in **Table 1** below. Prior to adding the volume of reconstituted Fabrazyme required for the patient dose, remove an equal volume of 0.9% Sodium Chloride Injection, USP from the infusion bag.

Table 1

Patient Weight (kg)	Minimum Total Volume (mL)
≤ 35	50
35.1 – 70	100
70.1 – 100	250
> 100	500

Patient dose (in mg) ÷ 5 mg/mL = Number of mL of reconstituted Fabrazyme required for patient dose

Example: Patient dose = 80 mg
80 mg ÷ 5 mg/mL = 16 mL of Fabrazyme

Slowly withdraw the reconstituted solution from each vial up to the total volume required for the patient dose. Inject the reconstituted Fabrazyme solution directly into the Sodium Chloride solution. Do not inject in the airspace within the infusion bag. Discard any vial with unused reconstituted solution.

5. Gently invert infusion bag to mix the solution, avoiding vigorous shaking and agitation.
6. Do not infuse Fabrazyme in the same intravenous line with other products.
7. Administer FABRAZYME using an in-line low protein binding 0.2 µm filter.

3 DOSAGE FORMS AND STRENGTHS

Fabrazyme is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or powder for reconstitution with Sterile Water for Injection, USP to yield a concentration of 5 mg/mL; and then further diluted with 0.9% Sodium Chloride Injection, USP for intravenous infusion.

Single-use vials are available in 35 mg and 5 mg dosages.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Allergic Reactions

Life-threatening anaphylactic and severe allergic reactions have been observed in patients during Fabrazyme infusions. Reactions have included localized angioedema (including swelling of the face, mouth, and throat), bronchospasm, hypotension, generalized urticaria, dysphagia, rash, dyspnea, flushing, chest discomfort, pruritus, and nasal congestion. Interventions have included cardiopulmonary resuscitation, oxygen supplementation, IV fluids, hospitalization, and treatment with inhaled beta-adrenergic agonists, epinephrine, and IV corticosteroids.

In clinical trials and postmarketing safety experience with Fabrazyme, approximately 1% of patients developed anaphylactic or severe allergic reactions during Fabrazyme infusion.

If anaphylactic or severe allergic reactions occur, immediately discontinue the administration of Fabrazyme and initiate necessary emergency treatment. Because of the potential for severe allergic reactions, appropriate medical support measures should be readily available when Fabrazyme is administered.

The risks and benefits of re-administering Fabrazyme following an anaphylactic or severe allergic reaction should be considered. Extreme care should be exercised, with appropriate medical support measures readily available, if the decision is made to re-administer the product *[see Warnings and Precautions (5.4) and Clinical Studies (14)]*.

5.2 Infusion Reactions

In clinical trials with Fabrazyme, approximately 50-55% of patients experienced infusion reactions during Fabrazyme administration, some of which were severe *[see Warnings and Precautions (5.1)]*. Severe infusion reactions experienced by more than one patient in clinical studies with Fabrazyme included chills, vomiting, hypotension, and paresthesia. Other infusion reactions included pyrexia, feeling hot or cold, dyspnea, nausea, flushing, headache, fatigue, pruritus, pain in extremity, hypertension, chest pain, throat tightness, abdominal pain, dizziness, tachycardia, nasal congestion, diarrhea, edema peripheral, myalgia, urticaria, bradycardia, and somnolence.

Most patients in clinical trials were pretreated with acetaminophen. In patients experiencing infusion reactions, pretreatment with an antipyretic and antihistamine is recommended. Infusion reactions occurred in some patients after receiving pretreatment with antipyretics, antihistamines, and oral steroids. Infusion reactions tended to decline in frequency with continued use of Fabrazyme. However, infusion reactions may still occur despite extended duration of Fabrazyme treatment. If an infusion reaction occurs, decreasing the infusion rate, temporarily stopping the infusion, and/or administrating additional antipyretics, antihistamines, and/or steroids may ameliorate the symptoms. If severe infusion reactions occur, immediate discontinuation of the administration of Fabrazyme should be considered, and appropriate medical treatment should be initiated. Severe reactions are generally managed with administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen, when clinically indicated. Because of the potential for severe infusion reactions, appropriate medical support measures should be readily available when Fabrazyme is administered. Patients who have experienced infusion reactions should be treated with caution when re-administering Fabrazyme.

5.3 Compromised Cardiac Function

Patients with advanced Fabry disease may have compromised cardiac function, which may predispose them to a higher risk of severe complications from infusion reactions *[see Warnings and Precautions (5.1) and (5.2)]*. Patients with compromised cardiac function should be monitored closely if the decision is made to administer Fabrazyme.

5.4 Immunogenicity and Re-challenge

In clinical trials with Fabrazyme, a few patients developed IgE antibodies or skin test reactivity specific to Fabrazyme. Two of six patients in the re-challenge study discontinued treatment with Fabrazyme prematurely due to recurrent infusion reactions. Four serious infusion reactions occurred in three patients during Fabrazyme infusions, including bronchospasm, urticaria, hypotension, and development of Fabrazyme-specific antibodies. Other infusion-related reactions occurring in more than one patient during the study included rigors, hypertension, nausea, vomiting, and pruritus. Physicians should consider testing for IgE antibodies in patients who experienced suspected allergic reactions and consider the risks and benefits of continued treatment in patients with anti-Fabrazyme IgE antibodies *[see Warnings and Precautions (5.1) and Dosage and Administration (2)]*.

Patients who have had a positive skin test to Fabrazyme or who have tested positive for Fabrazyme-specific IgE antibody have been re-challenged with Fabrazyme using a re-challenge protocol *[see Clinical Studies (14)]*. Re-challenge of these patients should only occur under the direct supervision of qualified personnel, with appropriate medical support measures readily available.

5.5 Monitoring: Laboratory Tests

There are no marketed tests for antibodies against Fabrazyme. If testing is warranted, contact your local Genzyme representative or Genzyme Corporation at (800) 745-4447.

6 ADVERSE REACTIONS

6.1 Adverse Reactions in Clinical Studies

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in patients in clinical practice.

The most serious adverse reactions reported with Fabrazyme treatment during clinical trials were anaphylactic and allergic reactions *[see Warnings and Precautions (5.1)]*.

The most common adverse reactions reported with Fabrazyme are infusion reactions, some of which were severe *[see Warnings and Precautions (5.1) and (5.2)]*. Serious and/or frequently occurring (≥ 5% incidence) related adverse reactions consisted of one or more of the following: chills, pyrexia, feeling hot or cold, dyspnea, nausea, flushing, headache, vomiting, paresthesia, fatigue, pruritus, pain in extremity, hypertension, chest pain, throat tightness, abdominal pain, dizziness, tachycardia, nasal congestion, diarrhea, edema peripheral, myalgia, back pain, pallor, bradycardia, urticaria, hypotension, face edema, rash, and somnolence. The occurrence of somnolence can be attributed to clinical trial specified pretreatment with antihistamines. Most infusion-related reactions requiring intervention were ameliorated with slowing of the infusion rate, temporarily stopping the infusion, and/or administration of antipyretics, antihistamines, or steroids.

Other reported serious adverse events included stroke, pain, ataxia, bradycardia, cardiac arrhythmia, cardiac arrest, decreased cardiac output, vertigo, hypoacousia, and nephrotic syndrome. These adverse events also occur as manifestations of Fabry disease; an alteration in frequency or severity cannot be determined from the small numbers of patients studied.

The data described below reflect exposure of 80 patients, ages 16 to 61 years, to 1 mg/kg Fabrazyme every two weeks in two separate double-blind, placebo-controlled clinical trials, for periods ranging from 1 to 35 months (mean 15.5 months). All 58 patients enrolled in one of the two studies continued into an open-label extension study of Fabrazyme treatment for up to 54 additional months. Patients were treated with antipyretics and antihistamines prior to the infusions.

Table 2 enumerates treatment-emergent adverse reactions (regardless of relationship) that occurred during the double-blind treatment periods of the two placebo-controlled trials (Study 1 and Study 2) *[see Clinical Studies (14)]*. Reported adverse reactions have been classified by Medical Dictionary for Regulatory Activities (MedDRA) terminology System Organ Class and Preferred Term.

Table 2

Summary of Adverse Reactions (regardless of relationship) Occurring in Fabrazyme®-Treated Patients at an Incidence Greater than 2.5% Compared to Placebo-Treated Patients

MedDRA System Organ Class/ Preferred Term	Fabrazyme® n=80 (%)	Placebo n=60 (%)
Cardiac Disorders		
Tachycardia	7 (9)	2 (3)
Ventricular wall thickening	4 (5)	1 (2)
Ear and Labyrinth Disorders		
Tinnitus	6 (8)	2 (3)
Hypoacusis	4 (5)	0
Gastrointestinal Disorders		
Toothache	5 (6)	2 (3)
Dry mouth	3 (4)	0
General Disorders and Administration Site Conditions		
Chills	34 (43)	7 (12)
Pyrexia	31 (39)	13 (22)
Fatigue	19 (24)	10 (17)
Edema peripheral	17 (21)	4 (7)
Pain	13 (16)	8 (13)
Feeling cold	9 (11)	1 (2)
Adverse event	8 (10)	3 (5)
Chest discomfort	4 (5)	1 (2)
Infections and Infestations		
Upper respiratory tract infection	35 (44)	18 (30)
Lower respiratory tract infection	14 (18)	4 (7)
Sinusitis	7 (9)	2 (3)
Pharyngitis	5 (6)	1 (2)
Fungal infection	4 (5)	0
Viral infection	4 (5)	0
Localized infection	3 (4)	0
Injury, Poisoning and Procedural Complications		
Procedural pain	20 (25)	12 (20)
Post-procedural complication	8 (10)	1 (2)
Excoriation	7 (9)	1 (2)
Fall	5 (6)	2 (3)
Contusion	3 (4)	0
Thermal burn	3 (4)	0
Investigations		
Blood creatinine increased	7 (9)	3 (5)
Musculoskeletal and Connective Tissue Disorders		
Pain in extremity	15 (19)	5 (8)
Back pain	13 (16)	6 (10)
Myalgia	11 (14)	3 (5)
Muscle spasms	4 (5)	1 (2)

Table 2, continued

Summary of Adverse Reactions (regardless of relationship) Occurring in Fabrazyme®-Treated Patients at an Incidence Greater than 2.5% Compared to Placebo-Treated Patients

MedDRA System Organ Class/ Preferred Term	Fabrazyme® n=80 (%)	Placebo n=60 (%)
Nervous System Disorders		
Headache	31 (39)	17 (28)
Paresthesia	25 (31)	11 (18)
Dizziness	17 (21)	5 (8)
Burning sensation	5 (6)	0
Psychiatric Disorders		
Anxiety	5 (6)	2 (3)
Depression	5 (6)	1 (2)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	26 (33)	15 (25)
Nasal congestion	15 (19)	9 (15)
Dyspnea	6 (8)	1 (2)
Respiratory tract congestion	6 (8)	1 (2)
Wheezing	5 (6)	0
Skin and Subcutaneous Tissue Disorders		
Rash	16 (20)	6 (10)
Pruritus	8 (10)	2 (3)
Vascular Disorders		
Hypertension	11 (14)	3 (5)
Hot flush	4 (5)	0

Observed adverse reactions in the Phase 1/2 study and the open-label treatment period for the extension study following the controlled study were not different in nature or intensity.

The safety profile of Fabrazyme in pediatric Fabry disease patients, ages 8 to 16 years, was found to be consistent with that seen in adults *[see Use in Specific Populations (8.4) and Clinical Studies (14)]*. The safety of Fabrazyme in patients younger than 8 years of age has not been evaluated.

6.2 Immunogenicity

Ninety-five of 121 (79%) adult patients and 11 of 16 (69%) pediatric patients (106 of 137, 74% of all patients) treated with Fabrazyme in clinical studies have developed IgG antibodies to Fabrazyme. Most patients who develop IgG antibodies do so within the first three months of exposure. IgG seroconversion in pediatric patients was associated with prolonged half-life of Fabrazyme, a phenomenon rarely observed in adult patients *[see Clinical Pharmacology (12.3) and Use in Specific Populations (8.4)]*. A possible cause for this prolongation likely pertains to the ability of antibodies to act as "carriers" for their antigens. Among the 14 female patients exposed to Fabrazyme in clinical studies, six (adult patients) developed IgG antibodies to Fabrazyme.

IgG antibodies to Fabrazyme were purified from 15 patients with high antibody titers (≥ 12,800) and studied for inhibition of *in vitro* enzyme activity. Under the conditions of this assay, most of these 15 patients had inhibition of *in vitro* enzyme activity ranging between 21-74% at one or more time points during the study. Assessment of inhibition of enzyme uptake in cells has not been performed. No general pattern was seen in individual patient reactivity over time. The clinical significance of binding and/or inhibitory antibodies to Fabrazyme is not known. In patients followed in the open-label extension study, reduction of GL-3 in plasma and GL-3 inclusions in superficial skin capillaries was maintained after antibody formation.

As with all therapeutic proteins, there is potential for immunogenicity. The data reflect the percentage of patients whose test results were considered positive for antibodies to Fabrazyme using an ELISA and radioimmunoprecipitation (RIP) assay for antibodies. The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Fabrazyme with the incidence of antibodies to other products may be misleading.

Testing for IgE antibodies was performed in approximately 60 patients in clinical trials who experienced moderate to severe infusion reactions or in whom mast cell activation was suspected. Seven of these patients tested positive for Fabrazyme-specific IgE antibodies or had a positive skin test to Fabrazyme. Patients who have had a positive skin test to Fabrazyme, or who have tested positive for Fabrazyme-specific IgE antibodies in clinical trials with Fabrazyme have been re-challenged *[see Clinical Studies (14), Warnings and Precautions (5.4) and Dosage and Administration (2)]*.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post approval use of FABRAZYME. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In postmarketing experience with agalsidase beta, severe and serious infusion-related reactions have been reported, some of which were life-threatening, including anaphylactic shock *[see Warnings and Precautions (5.1)]*. Reactions have included localized angioedema (including auricular swelling, eye swelling, dysphagia, lip swelling, edema, pharyngeal edema, face swelling, and swollen tongue), generalized urticaria, bronchospasm, and hypotension.

Adverse reactions (regardless of relationship) resulting in death reported in the postmarketing setting with FABRAZYME treatment included cardiorespiratory arrest, respiratory failure, cardiac failure, sepsis, cerebrovascular accident, myocardial infarction, renal failure, and pneumonia. Some of these reactions were reported in Fabry disease patients with significant underlying disease.

In addition to the adverse reactions reported in **Adverse Reactions in Clinical Studies (6.1)**, the following adverse reactions have been reported during postmarketing use of agalsidase beta: arthralgia, asthenia, erythema, hyperhidrosis, infusion site reaction, lacrimation increased, leukocytoclastic vasculitis, lymphadenopathy, hypoesthesia, oral hypoesthesia, palpitations, rhinorrhea, oxygen saturation decreased, and hypoxia.

7 DRUG INTERACTIONS

7.1 Interference with Other Drugs

No drug interaction studies were performed.

No *in vitro* metabolism studies were performed.

7.2 Interference with Laboratory Tests

There is no known interference by Fabrazyme with laboratory tests. Antibody samples should be collected prior to Fabrazyme infusions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B –

There are no adequate and well-controlled studies of Fabrazyme use in pregnant women. Reproduction studies performed in rats at doses up to 30 times the human dose have revealed no evidence of impaired fertility or negative effects on embryo fetal development due to Fabrazyme. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Women of childbearing potential should be encouraged to enroll in the Fabry patient registry. The registry will monitor the effect of Fabrazyme on pregnant women and their offspring. For more information, visit **www.fabryregistry.com** or call (800) 745-4447 *[see Patient Counseling Information (17)]*.

8.2 Labor and Delivery

There is no information on the effect of Fabrazyme during labor and delivery. Pregnant females are encouraged to enroll in the Fabry registry *[see Patient Counseling Information (17)]*.

8.3 Nursing Mothers

It is not known whether Fabrazyme is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Fabrazyme is administered to a nursing woman.

Nursing mothers should be encouraged to enroll in the Fabry registry *[see Use in Specific Populations (8.1) and Patient Counseling Information (17)]*.

8.4 Pediatric Use

The safety and efficacy of Fabrazyme were assessed in a multi-national, multi-center, uncontrolled, open-label study in 16 pediatric patients with Fabry disease (14 males, 2 females), ages 8 to 16 years *[see Clinical Studies (14)]*. Patients younger than 8 years of age were not included in clinical studies. The safety and efficacy in patients younger than 8 years of age have not been evaluated.

8.5 Geriatric Use

Clinical studies of Fabrazyme did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Responses in Women

Fabry disease is an X-linked genetic disorder. However, some heterozygous women will develop signs and symptoms of Fabry disease due to the variability of the X-chromosome inactivation within cells.

A total of 12 adult female patients with Fabry disease were enrolled in two separate randomized, double-blind, placebo-controlled clinical studies with Fabrazyme, and two female pediatric patients with Fabry disease, ages 11 years, were evaluated in an open-label, uncontrolled pediatric study *[see Use in Specific Populations (8.4) and Clinical Studies (14)]*. Although the safety and efficacy data available in female patients in these clinical studies are limited, there is no indication that female patients respond differently to Fabrazyme compared to males.

10 OVERDOSAGE

There have been no reports of overdose with Fabrazyme. In clinical trials, patients received doses up to 3 mg/kg body weight. The adverse reactions experienced by patients who received treatment with 3 mg/kg were similar to the adverse reactions experienced by patients who received treatment with 1 mg/kg.

11 DESCRIPTION

Fabrazyme (agalsidase beta) is a recombinant human α-galactosidase A enzyme with the same amino acid sequence as the native enzyme. Purified agalsidase beta is a homodimeric glycoprotein with a molecular weight of approximately 100 kD. The mature protein is comprised of two subunits of 398 amino acids (approximately 51 kD), each of which contains three N-linked glycosylation sites. α-galactosidase A catalyzes the hydrolysis of globotriaosylceramide (GL-3) and other α-galactyl-terminated neutral glycosphingolipids, such as galabiosylceramide and blood group B substances to ceramide dihexoside and galactose. The specific activity of Fabrazyme is approximately 70 U/mg (one unit is defined as the amount of activity that results in the hydrolysis of 1 µmole of a synthetic substrate, p-nitrophenyl-α-D-galactopyranoside, per minute under the assay conditions).

Fabrazyme is produced by recombinant DNA technology in a Chinese Hamster Ovary mammalian cell expression system.

Fabrazyme is intended for intravenous infusion. It is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or powder for reconstitution with Sterile Water for Injection, USP. Each 35 mg vial contains 37 mg of agalsidase beta, as well as 222 mg mannitol, 20.4 mg sodium phosphate monobasic monohydrate, and 59.2 mg sodium phosphate dibasic heptahydrate. Following reconstitution as directed, 35 mg of agalsidase beta (7 mL) may be extracted from each 35 mg vial.

Each 5 mg vial contains 5.5 mg of agalsidase beta, as well as 33.0 mg mannitol, 3.0 mg sodium phosphate monobasic monohydrate, and 8.8 mg sodium phosphate dibasic heptahydrate. Following reconstitution as directed, 5 mg of agalsidase beta (1 mL) may be extracted from each 5 mg vial.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fabry disease is an X-linked genetic disorder of glycosphingolipid metabolism. Deficiency of the lysosomal enzyme α-galactosidase A leads to progressive accumulation of glycosphingolipids, predominantly GL-3, in many body tissues, starting early in life and continuing over decades. Clinical manifestations of Fabry disease include renal failure, cardiomyopathy, and cerebrovascular accidents. Accumulation of GL-3 in renal endothelial cells may play a role in renal failure.

Fabrazyme is intended to provide an exogenous source of α-galactosidase A in Fabry disease patients. Nonclinical and clinical studies evaluating a limited number of cell types indicate that Fabrazyme will catalyze the hydrolysis of glycosphingolipids, including GL-3.

12.2 Pharmacodynamics

In a placebo-controlled study conducted in patients with Fabry disease after intravenous administration of 1 mg/kg of Fabrazyme every two weeks for 20 weeks, a reduction of GL-3 was observed in the capillary endothelium (vasculature) of kidney, heart and skin as determined by histological assessment, and in plasma as determined by ELISA *[see Clinical Studies (14)]*.

12.3 Pharmacokinetics

Plasma pharmacokinetic profiles of Fabrazyme were characterized at 0.3, 1, and 3 mg/kg in adult patients with Fabry disease. The area under the plasma concentration-time curve (AUC_{∞}) and the clearance (CL) did not increase proportionately with increasing doses, demonstrating that the enzyme follows non-linear pharmacokinetics (**Table 3**). Plasma pharmacokinetic profiles were also characterized in adult patients with Fabry disease given 1 mg/kg Fabrazyme every 14 days for a total of 11 infusions. Refer to **Table 3** below for more details.

In 15 pediatric Fabry patients (ranging in age from 8 to 16 years old and weighing between 27.1 to 64.9 kg) who were dosed with 1 mg/kg every 14 days, Fabrazyme pharmacokinetics were not weight-dependent (**Table 3**). Fabrazyme concentrations were about five times higher after IgG seroconversion, without any detectable impact on GL-3 clearance.

IgG seroconversion in pediatric patients was associated with prolonged half-life and plasma concentrations of Fabrazyme, a phenomenon rarely observed in adult patients. A possible cause for this prolongation likely pertains to the ability of antibodies to potentially act as "carriers" for their antigens *[see Adverse Reactions (6.2) and Use in Specific Populations (8.4)]*.

Table 3
Fabrazyme® Pharmacokinetic Summary

Dose	Regimen	Mean Infusion Length (min)	Infusion number (n= patients)	$AUC_{(0-\infty)}$ µg min/mL	C_{max} µg/mL	Half-life min	CL mL/ min/kg	Vss* mL/kg
Study FB9702-01: Phase 1/2 Study in Adult Patients with Fabry Disease								
0.3 mg/kg	q14 days x 5	132	1 (n=3)	79 ± 24	0.6 ± 0.2	92 ± 27	4.1 ± 1.2	225 ± 62
		128	5 (n=3)	74 ± 30	0.6 ± 0.2	78 ± 67	4.6 ± 2.2	330 ± 231
1 mg/kg	q14 days x 5	115	1 (n=3)	496 ± 137	5.0 ± 1.1	67 ± 12	2.1 ± 0.7	112 ± 13
		120	5 (n=2)	466 ± 382	4.74 ± 4.3	45 ± 3	3.2 ± 2.6	243 ± 236
3 mg/kg	q14 days x 5	129	1 (n=2)	4168 ± 1401	29.7 ± 14.6	102 ± 4	0.8 ± 0.3	81 ± 45
		300	5 (n=2)	4327 ± 2074	19.8 ± 5.8	87 ± 21	0.8 ± 0.4	165 ± 80
Study AGAL-1-002-98: Phase 3 Study in Adult Patients with Fabry Disease								
1 mg/kg	q14 days x 11	280	1-3 (n=11)	649 ± 226	3.5 ± 1.6	89 ± 20	1.8 ± 0.8	120 ± 80
		280	7 (n=11)	372 ± 223	2.1 ± 1.14	82 ± 25	4.9 ± 5.6	570 ± 710
		300	11 (n=11)	784 ± 521	3.5 ± 2.2	119 ± 49	2.3 ± 2.2	280 ± 230
Study AGAL-016-01: Phase 2 Study in Pediatric Patients with Fabry Disease								
1 mg/kg	q14 days x 24	208	1 (n=8-9)	344 ± 307	2.2 ± 1.9	86 ± 27	5.8 ± 4.6	1097 ± 912
		111	12 (n=15)	1007 ± 688	4.9 ± 2.4	130 ± 41	1.6 ± 1.2	292 ± 185
		108	24 (n=9-10)	1238 ± 547	7.1 ± 4.4	151 ± 59	1.1 ± 0.8	247 ± 146

All data reported as the mean ± standard deviation.
*Vss = volume of distribution at steady state

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or human studies to assess the carcinogenic or mutagenic potential of Fabrazyme. There are no studies assessing the potential effect of Fabrazyme on fertility in humans.

14 CLINICAL STUDIES

The safety and efficacy of Fabrazyme were assessed in four clinical studies in patients with Fabry disease.

Study 1 was a randomized, double-blind, placebo-controlled, multi-national, multi-center study of 58 Fabry patients (56 males and 2 females), ages 16 to 61 years, all naïve to enzyme replacement therapy. Patients received either 1 mg/kg of Fabrazyme or placebo every two weeks for five months (20 weeks) for a total of 11 infusions. All patients were pretreated with acetaminophen and an antihistamine to decrease or prevent infusion reactions. Oral steroids were an additional option to the pretreatment regimen for patients who exhibited severe or recurrent infusion reactions. The primary efficacy endpoint of GL-3 inclusions in renal interstitial capillary endothelial cells, was assessed by light microscopy and was graded on an inclusion severity score ranging from 0 (normal or near normal) to 3 (severe inclusions).

A GL-3 inclusion score of 0 was achieved in 20 of 29 (69%) patients treated with Fabrazyme compared to 0 of 29 treated with placebo (p<0.001). Similar reductions in GL-3 inclusions were observed in the capillary endothelium of the heart and skin (**Table 4**). No differences between groups in symptoms or renal function were observed during this five-month study.

Table 4
Reduction of GL-3 Inclusions to Normal or Near Normal Levels (0 Score) in the Capillary Endothelium of the Kidney, Heart, and Skin

	5 Months of the Controlled Study		6 Months of the Open-label Extension Study	
	Placebo (n=29)	Fabrazyme® (n=29)	Placebo/Fabrazyme® (n=29)*	Fabrazyme®/Fabrazyme® (n=29)*
Kidney	0/29	20/29	24/24	23/25
Heart	1/29	21/29	13/18	19/22
Skin	1/29	29/29	25/26	26/27

* Results reported where biopsies were available

All 58 patients in Study 1 participated in an open-label extension study of Fabrazyme at 1 mg/kg every two weeks, which continued for an additional 54 months. At the end of six months of open-label treatment, most patients achieved a GL-3 inclusion score of 0 in capillary endothelium (**Table 4**). GL-3 was decreased to normal or near normal levels in mesangial cells, glomerular capillary endothelium, interstitial cells, and non-capillary endothelium. GL-3 deposition was still present in vascular smooth muscle cells, tubular epithelium and podocytes, at variably reduced levels. Forty-four of the 58 patients completed 54 months of the open-label extension study. Thirty-six of these 44 patients underwent follow-up skin biopsy, and 31 of these patients showed sustained GL-3 clearance in the capillary endothelium of the skin. Follow-up heart and kidney biopsies were assessed in only 8 of the 44 patients, which showed sustained GL-3 clearance in the capillary endothelium of the kidney in 8 patients, and sustained GL-3 clearance in the capillary endothelium of the heart in 6 patients. Plasma GL-3 levels were reduced to normal levels (≤ 7.03 µg/mL determined by LC/MS/MS) and remained at normal levels after up to 60 months of treatment. The reduction of GL-3 inclusions suggests that Fabrazyme may ameliorate disease expression; however, the relationship of GL-3 inclusion reduction to specific clinical manifestations of Fabry disease has not been established.

Study 2 was a randomized (2:1 Fabrazyme to placebo), double-blind, placebo-controlled, multi-national, multi-center study of 82 patients (72 males and 10 females), ages 20 to 72 years, all naïve to enzyme replacement therapy. Patients received either 1 mg/kg of Fabrazyme or placebo every two weeks for up to a maximum of 35 months (median 18.5 months). There was significant difference in post-baseline plasma GL-3 levels in the Fabrazyme-treated patients compared to placebo. The reduction in plasma GL-3 levels in the Fabrazyme group compared to the placebo group was significant at one year (p<0.0001) and at two years (p=0.0019). Fourteen patients (8 in Fabrazyme-treated and 6 in placebo) had skin biopsies at first infusion and final visit. All Fabrazyme-treated patients had capillary endothelium and deep vessel endothelium scores of zero at the final visit. Four (4) of 6 placebo patients had non-zero capillary endothelium scores (p=0.0150), and 6 of 6 had non-zero deep vessel endothelium scores (p=0.0003).

Sixty-seven patients who participated in Study 2 were subsequently entered into an open-label extension study in which all patients received 1 mg/kg of Fabrazyme every two weeks for up to a maximum of 18 months. There was a statistically significant reduction in mean plasma GL-3 levels with durability in effect through the additional 18 months of treatment in the extension study from pretreatment baseline.

Study 3 (Pediatric Study) was an open-label, uncontrolled, multi-national, multi-center study to evaluate safety, pharmacokinetics, and pharmacodynamics of Fabrazyme treatment in 16 pediatric patients with Fabry disease (14 males, 2 females), who were ages 8 to 16 years at first treatment. All patients received Fabrazyme 1 mg/kg every two weeks for up to 48 weeks. At baseline, all 14 males had elevated plasma GL-3 levels (i.e., > 7.03 µg/mL), whereas the two female patients had normal plasma GL-3 levels. Twelve of the 14 male patients, and no female patients, had GL-3 inclusions observed in the capillary endothelium on skin biopsies at baseline. At Weeks 24 and 48 of treatment, all 14 males had plasma GL-3 within the normal range. The 12 male patients with GL-3 inclusions in capillary endothelium at baseline achieved GL-3 inclusion scores of 0 at Weeks 24 and 48 of treatment. The two female patients' plasma GL-3 levels remained normal through study Week 48.

No new safety concerns were identified in pediatric patients in this study, and the overall safety and efficacy profile of Fabrazyme treatment in pediatric patients was found to be consistent with that seen in adults. Immunologic responses in pediatric patients may differ from those in adults, as IgG seroconversion in pediatric patients was associated with prolonged half-life concentrations of Fabrazyme, a phenomenon rarely observed in adult patients *[see Clinical Pharmacology (12.3), Adverse Reactions (6.2), and Use in Specific Populations (8.4)]*.

Study 4 was an open-label, re-challenge study to evaluate the safety of Fabrazyme treatment in patients who had a positive skin test to Fabrazyme or who had tested positive for Fabrazyme-specific IgE antibodies. In this study, six adult male patients, who had experienced multiple or recurrent infusion reactions during previous clinical trials with Fabrazyme, were re-challenged with Fabrazyme administered as a graded infusion, for up to 52 weeks of treatment *[see Warnings and Precautions (5.4)]*. The initial two re-challenge doses of Fabrazyme were administered as a 0.5 mg/kg dose per week at an initial infusion rate of 0.01 mg/min for the first 30 minutes (1/25th the usually recommended maximum infusion rate). The infusion rate was doubled every 30 minutes thereafter, as tolerated, for the remainder of the infusion up to a maximum rate of 0.25 mg/min. If the patient tolerated the infusion, the dose was increased to 1 mg/kg every two weeks (usually recommended dose), and the infusion rate was increased by slow titration upwards *[see Dosage and Administration (2)]*. Four of the six patients treated in this study received at least 26 weeks of study medication, and two patients discontinued prematurely due to recurrent infusion reactions *[see Warnings and Precautions (5.4)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

Fabrazyme is supplied as a sterile, nonpyrogenic, white to off-white lyophilized cake or powder. Fabrazyme 35 mg vials are supplied in single-use, clear Type I glass 20 mL (cc) vials. The closure consists of a siliconized butyl stopper and an aluminum seal with a plastic purple flip-off cap. Fabrazyme 5 mg vials are supplied in single-use, clear Type I glass 5 mL (cc) vials. The closure consists of a siliconized butyl stopper and an aluminum seal with a plastic gray flip-off cap.

35 mg vial: NDC 58468-0040-1
5 mg vial: NDC 58468-0041-1

Refrigerate vials of Fabrazyme at 2° to 8°C (36° to 46°F). DO NOT USE Fabrazyme after the expiration date on the vial. Reconstituted and diluted solutions of Fabrazyme should be used immediately. This product contains no preservatives. If immediate use is not possible, the reconstituted and diluted solution may be stored for up to 24 hours at 2° to 8°C (36° to 46°F).

17 PATIENT COUNSELING INFORMATION

Patients should be informed that a Registry has been established in order to better understand the variability and progression of Fabry disease in the population as a whole and in women *[see Use in Specific Populations (8.6)]*, and to monitor and evaluate long-term treatment effects of Fabrazyme. The Registry will also monitor the effect of Fabrazyme on pregnant women and their offspring. Patients should be encouraged to participate and advised that their participation is voluntary and may involve long-term follow-up. For more information, visit **www.fabryregistry.com** or call (800) 745-4447.

Fabrazyme is manufactured and distributed by:
Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
1-800-745-4447 (phone)

U.S. License Number: 1596

5031 (07/10)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 October 2010
EMA/CHMP/654389/2010
Press Office

Press release

European Medicines Agency reviews treatment recommendations for Fabrazyme

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has reviewed its previous recommendations on the use of Fabrazyme (agalsidase beta) during the ongoing supply shortage. This was triggered by an increase in reported adverse events in patients treated with the lower dose of Fabrazyme that has been introduced during the shortage.

Fabrazyme is used to treat the rare, inherited enzyme-deficiency disorder Fabry disease. Temporary treatment recommendations to manage patients relying on this medicine have been in place since the start of the supply shortage and have been regularly updated.

The CHMP is now recommending that physicians switch back to prescribing the full dose of Fabrazyme according to the authorised product information, depending on the availability of enzyme replacement therapy and the severity of the disease.

In making their recommendation, the Committee took the outcome of a consensus group of experts in Fabry disease into account. The group met twice in October 2010, and included physicians with experience in Fabry disease and patient representatives working together to prioritise patients with Fabry disease during the ongoing supply shortage. The Committee also looked at spontaneous reports of adverse events and data from the Fabry registry.

The CHMP noted that since the introduction of a lower dose of Fabrazyme in June 2009, there has been a steady increase in the number of reported adverse events, matching the increase in the number of patients on the lower dose. At first, most of the events were pain-related, soon followed by reports of events affecting the heart, the central nervous system and the kidneys. This pattern suggests a progression of Fabry disease. Recently, a decrease in number of reported adverse events has been observed, which reflects the fact that more patients have either been switched to Replagal or have started receiving a full dose of Fabrazyme again. Despite this, the Committee observed that a subgroup of patients seems to be doing well on the lower Fabrazyme dose.

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The CHMP also noted that monitoring plasma or urine GL-3 levels does not appear to add value to the clinical management of the patients while on a lower dose.

The updated CHMP temporary treatment recommendations for Fabrazyme are as follows:

- Patients who require enzyme replacement therapy for Fabry disease should be prescribed the authorised dose of either Fabrazyme (1.0 mg/kg once every two weeks) or Replagal (0.2 mg/kg once every two weeks).
- Low doses of Fabrazyme should be limited to those patients who are stable and prefer to remain on a low dose.
- Patients and prescribers are advised that a deterioration of the condition has been observed in patients on the lower dose. Pain, cardiac manifestations and deafness are the usual manifestations of Fabry disease progression.

These recommendations do not change the currently approved product information for Fabrazyme.

The supply shortage of Fabrazyme began in June 2009 and was caused by a series of manufacturing problems at the production site in Allston Landing, in the United States of America. Because the current productivity at Allston Landing is still lower than expected, supply of Fabrazyme will not return to normal before the second half of 2011, according to Genzyme.

The CHMP remains concerned about the continued supply shortages of Genzyme's medicines and is closely monitoring the implementation of their improvement measures to prevent similar manufacturing and quality problems in the future.

The Agency will make further updates as appropriate.

Notes

1. This press release together with all relevant documents is available on the European Medicines Agency's web site here.
2. The CHMP assessment report on the supply shortage of Fabrazyme between June 2009 and September 2010 will be published on the European Medicines Agency's website shortly.
3. The treatment recommendations of the consensus group of the experts in Fabry disease are in line with the currently authorised product information of Fabrazyme, and will be published in a peer-reviewed scientific journal.
4. The previous treatment recommendations of the CHMP for Fabrazyme were made on 6 July 2010, following continued supply shortage.
5. Initially, the supply shortage for Fabrazyme was caused by the shutting down of Genzyme's production site in Allston Landing, in the United States of America, for the sanitisation of the bioreactors due to a viral contamination.
6. More information on Fabrazyme, including the currently approved product information, is available in the European public assessment report (EPAR).
7. More information on the work of the European Medicines Agency, can be found on the Agency's website: www.ema.europa.eu

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report

for

FABRAZYME

agalsidase beta

Assessment report on the shortage of Fabrazyme'
Overview of Shortage Period: Spontaneous Reports from June 2009 through 15 September 2010 and Registry Data from June 2009 through 05 August 2010

EMEA/H/C/000370

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An agency of the European Union

I. INTRODUCTION

Fabry's disease is a lysosomal storage disorder due to a deficiency in alpha-galactosidase A. The natural course of the disease is illustrated in figure 1.

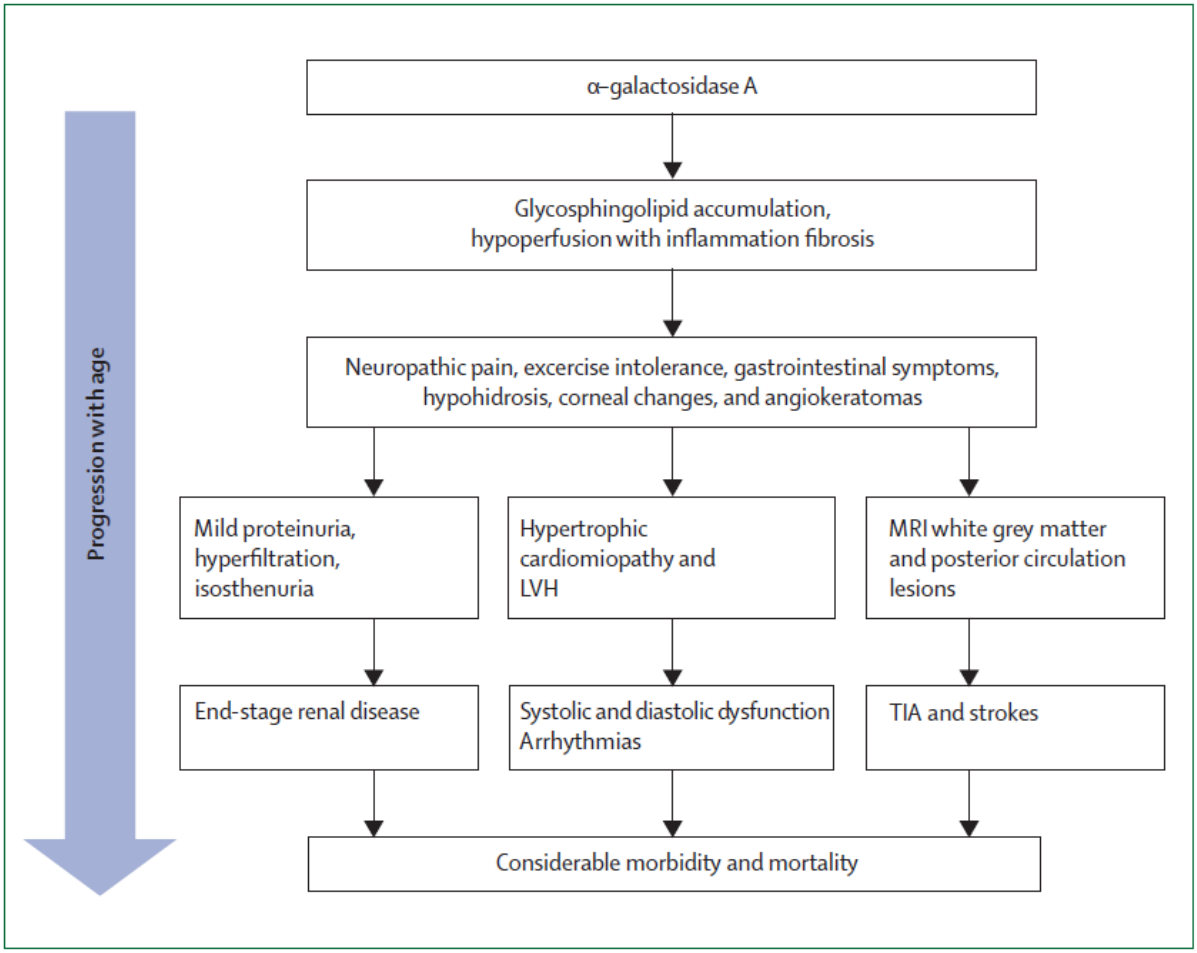


Figure 1: **Progression of clinical findings in Fabry's disease with age**
Progression of any of the paths depicted can proceed independently from the others, which means that for some patients, cardiac disease will be the most severe whereas for others renal or CNS disease can predominate. LVH=left ventricular hypertrophy. TIA=transient ischaemic stroke.

(Zarate & Hopkin. Lancet 2008;372:1427-35)

At the start of the disease (during the first decades of life), the main manifestations are pain (crises) and gastrointestinal symptoms. The long-term progression of Fabry disease is associated with chronic renal disease, cardiovascular disease, and cerebrovascular events (during fifth decade of life); this deterioration is a major cause of morbidity and mortality.

Fabrazyme® is an enzyme replacement therapy for Fabry's disease. The recommended dose and frequency in section 4.2 of the SmPC is 1 mg/kg every other week (eow).

Since June 2009 there has been a shortage of supply of Fabrazyme (agalsidase beta) because of production and quality (GMP) problems. To date four Direct Healthcare Professional Communications (DHPCs) with dose recommendations have been released in the European Union (EU):

<u>25 June 2009:</u>

- Children and adolescents less than 18 years old as well as adult male Fabry patients to continue with recommended Fabrazyme dosing and frequency.
- Adult female Fabry disease patients with no evidence of clinically significant end organ damage to be treated with a reduced dose of 0.3-0.5 mg/kg every 2 weeks.

28 September 2009:

- Children and adolescents less than 18 years old to continue with recommended Fabrazyme dosing and frequency.
- Adult male patients already treated and stabilized to receive 0.3 mg/kg every 2 weeks (as for adult female patients).
- Patients should be followed up every two months, and plasma or urinary globotriaosylceramide (GL-3) levels should be closely monitored.
- Patients who demonstrated a deterioration of disease should be switched back to their original dosage regimen with Fabrazyme.

22 April 2010:

- Treatment recommendations as communicated in the DHPC of September 2009 remained in place.
- For patients experiencing aggravation of disease symptoms and/or AEs ascribed to the lowered dose of Fabrazyme, physicians were advised to switch their treatment back to their original dosing regimen or initiate treatment with an alternative approved medicinal product.

09 July 2010:

- No new patients should be started on Fabrazyme, if alternative treatment is available.
- For patients on a dose lower than the recommended dose, physicians should consider switching to an alternative treatment, such as Replagal.
- Where alternative treatment is not available or where (continuation of) treatment with Fabrazyme is deemed medically necessary, it is important to note that an increase in clinical manifestations indicative of Fabry disease progression has been observed with the lowered dose.

In the United States all patients were asked to reduce their Fabrazyme use by spreading out their usual dose over a longer period of time.

During the shortage period, the MAH has updated the Rapporteur with reports on spontaneous reporting and data from the Fabry registry. These data and the Rapporteur's conclusions are summarized in this assessment report.

On 4 and 9 October 2010 a consensus meeting took place of representatives of physicians treating Fabry disease in the EU. At that meeting treatment recommendations in times of shortage were agreed. A representative of the EMA was present as an observer.

The purpose of this assessment report is to present an overview of the data received so far on patients on a lower dose of Fabrazyme.

II. POSSIBLE DETERIORATION IN PATIENTS ON THE LOWERED DOSE

The Rapporteur has reviewed all data from spontaneous reports regarding patients who reported adverse events (AEs) assessed to be suggestive of clinical deterioration on a lowered dose of Fabrazyme (from Genzyme's Global Patient Safety and Risk Management department (GPS&RM) database) for the period from 25 June 2009 through 15 September 2010.
In addition, all information from the Fabry Registry regarding certain clinical characteristics of patients whose doses of Fabrazyme were lowered during a period of approximately 13 months, from 25 June 2009 through 05 August 2010 have been reviewed and the data from both sources have been compared.

In all cases, it was assumed that these patients' doses were lowered in response to the reduction in the global supply of Fabrazyme during this period.

The MAH considered the following:

A. All spontaneous cases reported to GPS&RM and medically reviewed from 25 June 2009 through 15 September 2010 were considered for the analysis of patients experiencing clinical deterioration on a lower dose of Fabrazyme if they met the following three criteria:
1. The reported AE occurred after 25 June 2009,
2. The patient was on a lowered dose of Fabrazyme due to the supply shortage, and
3. The AE was not an infusion associated reaction (IAR).

B. After selecting the cases that met these criteria, the narratives were screened by the MAH for information with regard to evidence of clinical deterioration. A medical review of these cases, which included all relevant medical history and available laboratory data, was performed by GPS&RM to determine whether the AEs were suggestive of potential clinical deterioration. Due to the ongoing limited supply, cases of patients with clinical deterioration but without complete documentation of a lowered dose have also been incorporated into the reports; further efforts are being made with the patient's health care professional (HCP) to confirm the dose reduction in these cases.

C. Events assessed to be suggestive of potential clinical deterioration after medical review included, but were not limited to: cardiovascular events such as arrhythmia, coronary artery disease or heart failure; cerebrovascular events such as transient ischaemic attacks or cerebrovascular accidents; renal events such as renal impairment or renal failure; gastrointestinal events such as abdominal pain, nausea, vomiting, and diarrhoea; events consistent with Fabry disease-related pain such as paraesthesias, pain in extremities, or peripheral neuropathy; changes in hearing; and constitutional symptoms such as fatigue and malaise.

Physicians who enrol patients in the Fabry Registry are asked to monitor patients and submit clinical data according to a Minimum Recommended Schedule of Assessments. This schedule includes key clinical and laboratory parameters that should be evaluated and the frequency at which they should be reported to the Fabry Registry. However, Genzyme has found that these data are typically entered on a semi-annual or annual basis. In addition, not all changes in dosage have been reported to the Fabry Registry and changes in the average reported dose may not accurately reflect patients' actual treatment regimens.

Events of chronic renal disease, cardiovascular disease, cerebrovascular events, and deaths reported to the Fabry Registry were investigated in patients whose doses were lowered during the period from 25 June 2009 through 05 August 2010. In addition, data related to peripheral pain, abdominal pain, and diarrhoea were included. Reported plasma and urine levels of GL-3 were also analyzed in patients who are enrolled in the Fabry Registry.

III. REVIEW OF DATA FROM SPONTANEOUS REPORTS

The MAH submits bi-weekly reports on patients all over the world. Most reports are on non-EU patients. In every report, the MAH is required to discuss the EU patients separately.

In the EU, of the patients on Fabrazyme, approximately 4% was on a dose lower than 1 mg/kg/eow prior to the start of the supply shortage.
After a decline, the number of patients on Fabrazyme as well as the number of patients on the lowered dose seems to have stabilized. This is an indication that the recommendations are being followed to some extent and that no or a small number of new patients are being initiated on Fabrazyme.
In the figure below, the bars indicate the numbers of reported AEs. The figure only presents the unique patients, so the real number of AEs is higher because for some patients there are more AE reports in time received. There appears to be a stabilisation in the number of AEs, suggesting that patients who still are on the lowered dose, are relatively stable and are not adversely affected by the use of the lowered dose.

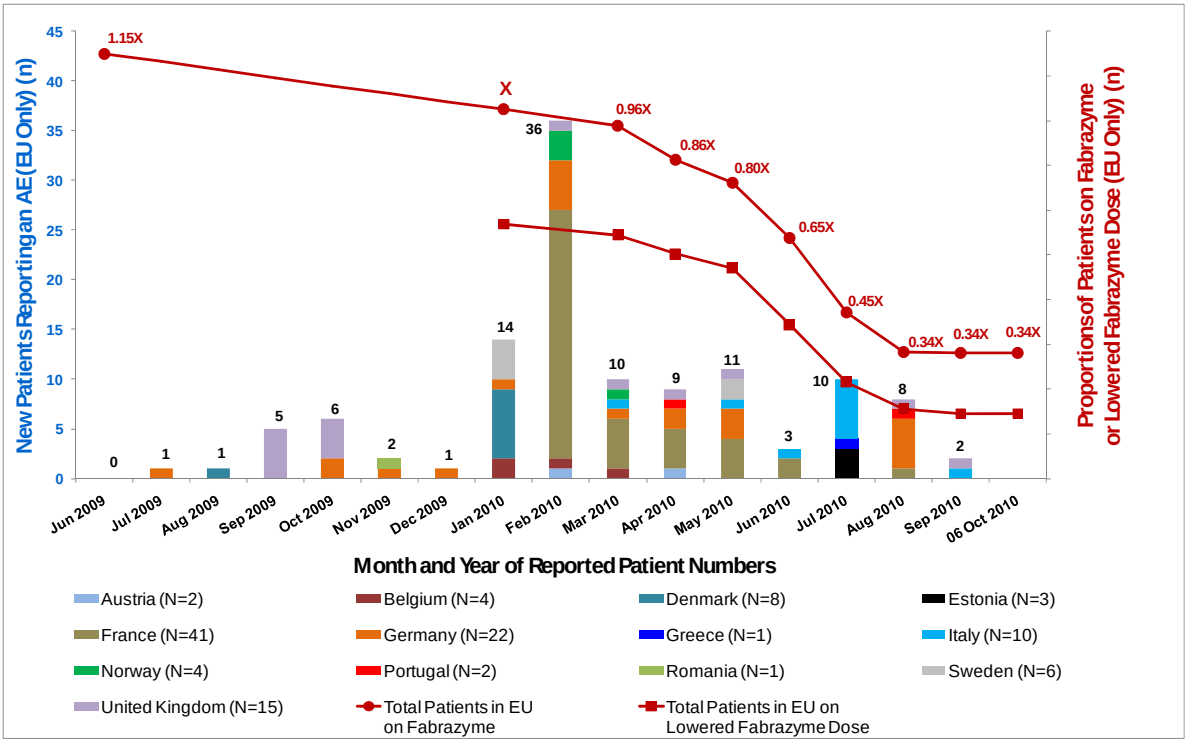
See table 1 and figure 2 below.

Table 1: ***Estimated Percentage of Patients in the European Union on a Lower Dose***

Estimated Number of:	January 2010	March 2010	April 2010	May 2010	June 2010	July 2010	August 2010	Sept. 2010	06 Oct. 2010
Patients on Fabrazyme*	x	0.96x	0.86x	0.80x	0.65x	0.45x	0.34x	0.34x	0.34x
Patients on 1 mg/kg/eow	26%	26%	25%	23%	31%	37%	37%	41%	41%
Pediatric patients on 1 mg/kg/eow	5%	5%	5%	5%	5%	6%	7%	7%	7%
Patients on 0.5 mg/kg/eow	32%	22%	23%	22%	21%	6%	13%	12%	12%
Patients on 0.3 mg/kg/eow	36%	47%	47%	50%	43%	51%	42%	40%	40%

*Note that x=total number of patients on Fabrazyme per January 2010 (exact number not disclosed for confidentiality reasons). In time, this number gradually decreases.

Figure 2 New Unique Patients Reporting AEs Assessed to be Potentially Suggestive of Clinical Deterioration on a Lowered Dose of Fabrazyme by Country, and Proportions of Patients on Fabrazyme and Lowered Doses of Fabrazyme (EU Patients Only) Since the Start of the shortage



* Bar graph data in Figure 1 represent the total number of unique patients by month who are new to the analysis of case reports assessed to be suggestive of potential clinical deterioration on a lowered dose of Fabrazyme. All patients new to the analysis during the current biweekly period are presented in that month. However, in subsequent reports, the patients will be listed in the month of the worldwide receipt date (WWRD) of their AE report. For example, if a case was initially reported with a WWRD in February 2010, but the data confirming that the patient was on a lowered dose were not received and medically reviewed until 20 September 2010, the case would be presented for the first time in the 16 September 2010 through 30 September 2010 biweekly report in the column for 16-30 September 2010. This presentation shows how many new unique patients from the EU are reporting AEs assessed to be suggestive of clinical deterioration on a lowered dose of Fabrazyme during the recent biweekly period. However, in subsequent reports, the case would be presented in the February 2010 column based on the initial WWRD to the safety database. Further, each unique patient is counted in Figure 1 only once. Therefore, if a patient reports one AE in September 2009 and another separate AE in March 2010, the patient will be included in the calculations for September 2009 only.

** The AEs received and medically reviewed after 30 September 2010 are beyond the scope of this document and will be presented in future reports.

There is a clear trend of increasing reports of (serious) AEs since the shortage. The higher the percentage of patients receiving the lowered dose, the higher the number of AEs reported. After the recommendations to switch to Replagal or to return to a higher dose when clinical deterioration appeared, this percentage decreased, as well the absolute number of reports. A subgroup of patients seems to be doing well on the lower Fabrazyme dose.

The MAH did not provide comparable data for the period before the shortage and concluded that based on the limited data available, it is not possible to ascertain whether more patients are having serious clinical events while on lowered doses of Fabrazyme, compared with earlier data from patients on a full dose of Fabrazyme.
However, the MAH did provide and compare quarterly data from Q3 2009 (see table 1). The percentage of AEs ascribed to the lowered dose increased steeply. After the increase in AEs seen from Q4 2009 to Q1 2010, the number of reported AEs from Q1 2010 to Q2 2010 appears to have been either stabilizing or decreasing.
Over time, increases have been seen in serious cardiac and nervous AEs and, to a lesser extent, in renal events, while a decrease, albeit less steep, has been seen in reported AEs related to pain/pareasthesias.
The reported AEs are summarised in table 2. This table concerns data up to Q3 2010.
Note that this table presents worldwide data.

Table 2 Summary of Patients and Adverse Events Spontaneously Reported to Genzyme's Global Patient Safety & Risk Management Database That Were Received and Medically Reviewed from 25 June 2009 through 30 September 2010 and Assessed as Being Suggestive of Clinical Deterioration while on a Lowered Dose of Fabrazyme (selection of SOCs)

Adverse event category Preferred Term	Q3 2009 (N=21)		Q4 2009 (N=34)		Q1 2010 (N=89)		Q2 2010 (N=90)		Q3 2010	
	Events (n)	Patients (n)	Events (n)	Patients (n)	Events (n)	Patients (n)	Events (n)	Patients (n)	Events (n)	Patients (n)
Cardiac disorders (arrhythmias, cardiac failure, cardiac occlusion, MI)	1	1	1	1	13	12	14	14	11	10
Cerebrovascular-stroke	1	1	2	2	7	7	2	2	10	7
Fabry disease related pain	10	9	10	9	41	41	35	35	24	21
Gastrointestinal pain	2	2	5	5	3	3	5	4	7	7
Gastrointestinal diarrhoea	2	2	5	5	5	5	4	4	1	1
Renal disorders (renal failure, renal failure chronic)	-	-	-	-	6	6	4	4	9	9

 # The above data come from: a) Genzyme's "Report on Fabry Registry Patients who received Fabrazyme Dose reductions between 25 June 2009 and 05 August 2010 and Comparison to Spontaneous reports to Global Patients Safety and Risk Management Database" dated 23 September 2010; b) data from the third quarter 2010 (obtained from the biweekly reports 01-15 July; 16-31 July; 01-15 August; 16-31 August; 01-15 September; 16-30 September 2010.

Patients returning to higher dose or switched to Replagal
Some information was received on patients who had been switched to Replagal. However, the data is limited and no conclusions can be drawn from them.
There were also switches between Replagal and Fabrazyme prior to the Fabrazyme supply shortage.

GL-3 levels
There are some data available on GL-3 levels measured in patients before and after their dose lowering. These data do not show any clear trend.

IV. REVIEW OF DATA FROM FABRY REGISTRY

In the Fabry Registry, 410 patients were reported to be on lowered dose (US 59% and Europe 22%).
As of 5 August 2010, the Registry had enrolled a total of 3,681 Fabry patients (1,808 males and 1,873 females), irrespective whether or not they received enzyme replacement therapy.

Cerebrovascular events: The stroke incident rates have increased slightly since 25 June 2009 (from 0.63 (95% CI: 0.31–1.12) per 100 person years of follow-up to 1.32 (95% CI: 0.36–3.37).

Renal events: Since the previous Registry report, one new case of a renal event was reported (initiation of chronic dialysis). The incidence rate in these very small numbers did not increase during the shortage.

Cardiovascular events: The number of patients who had cardiovascular events after 25 June 2009 was small (N=3) and the observation period was short. Therefore, no conclusion can be made on whether or not there is any meaningful difference in the incidence of cardiovascular events in Fabrazyme-treated patients before and after 25 June 2009.

Neurologic peripheral pain, abdominal pain, diarrhoea: There have been consistent reports of a higher percentage of patients reporting peripheral pain, abdominal pain and diarrhoea on a daily basis after 25 June 2009, compared with the period before that date.

Globotriaosylceramide (GL-3) levels: The findings on the plasma GL-3 data are comparable with those in the spontaneous reporting; there is no apparent change.
Regarding urine GL-3 levels, six of the seven patients had lower levels post June 2009 compared with pre June.

V. CONSENSUS MEETING

On 4 and 9 October 2010, a consensus meeting of treating physicians was held. The purpose of that meeting was to reach consensus on the proper management of Fabry disease during the period of shortage of enzyme replacement therapy (ERT) and to come up with clear treatment recommendations for physicians during the shortage period of Fabrazyme (shortage of agalsidase beta and subsequent constraints in supply of agalsidase alfa). The aim was also to have the agreed treatment recommendations published in a scientific journal.
The EMA was present as an observer and the CHMP was informed of the outcomes of the meeting by the physicians' representative.

The CHMP took the outcome of this consensus group of experts into account.

VI. CONCLUSIONS

- There is a clear trend of increasing reports of (serious) AEs since the start of the shortage. The higher the percentage of patients receiving the lowered dose, the higher the number of AEs reported. After the recommendations to switch to Replagal or to return to a higher dose when clinical deterioration appeared, this percentage, as well the absolute number of reports, decreased. This provides a picture of more and more patients at risk from the lowered dose switching back to higher dose or to Replagal.

- A certain patient subgroup seems to have no obvious clinical effects due to the lowered dose.

- The safety data on the registry period June 2009 to 05 August 2010 confirm the trends as seen in the spontaneous reports. Due to its voluntary-based and periodic reporting, the Registry is somewhat 'behind' in time and this is reflected in the data. In the Registry so far the increases and decreases described above are still developing.

- Taking into account the potential for increased awareness of the supply shortage among healthcare providers which could potentially lead to reporting biases, the limitations of spontaneous reporting and the small number of reports, there is an increase in reporting of adverse events possibly due to the lowered dose. In the early stages of the shortage the main increases in AEs were related to pain/paresthesia events, while later on in the shortage period, the main increases were in serious cardiac events such as myocardial infarction, in serious nervous disorders such as stroke, and – possibly to a lesser extent – in renal disorders. There have been consistent reports of a higher percentage of patients reporting peripheral pain, abdominal pain and diarrhoea on a daily basis after 25 June 2009 (start of the shortage).

- **This pattern of adverse events resembles the natural, but accelerated, course of Fabry's disease.**

- The CHMP requests the MAH to include this important data on long-term low dosage use in the SPC in section 5.1. The MAH should provide wording stating that during the shortage period, spontaneous reports on the following adverse events (indicating a deterioration of the disease) were received: Fabry disease-related pain, paresthesia, diarrhoea, cardiac disorders as arrhythmias and myocardial infarction, nervous system disorders as stroke, and renal disorders as renal failure.

- A yet unexplained finding is that the plasma GL-3 levels show no apparent change before and after dose lowering. Data on the urine GL-3 levels are scarce; in six of the seven patients there was a lowering after dose lowering.

JS 44 (Rev. 12/07)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS
Hochendoner, Anita; Hochendoner, Earl; Bova, Anita; Carik, Joseph M.; Carik, Barbara J.; Britton, Amber; Britton, Shawn; Britton, Cheryl; Olzewski, Thomas; and Roberts, David

(b) County of Residence of First Listed Plaintiff Allegheny
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorney's (Firm Name, Address, and Telephone Number)
Matthew L. Kurzweg, Esq., Kurzweg Law Offices, 945 Liberty Avenue, 5th Floor Bruno Building, Pittsburgh, PA , 15222. (412) 258-2223

DEFENDANTS
Genzyme Corporation; and Mount Sinai School of Medicine of the City University of New York

County of Residence of First Listed Defendant
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED.

Attorneys (If Known)

II. BASIS OF JURISDICTION (Place an "X" in One Box Only)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant)
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT (Place an "X" in One Box Only)

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury - Med. Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence

Habeas Corpus:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt.Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

IMMIGRATION
- ☐ 462 Naturalization Application
- ☐ 463 Habeas Corpus - Alien Detainee
- ☐ 465 Other Immigration Actions

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☐ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☒ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes

V. ORIGIN (Place an "X" in One Box Only)

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from another district (specify) ☐ 6 Multidistrict Litigation ☐ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing **(Do not cite jurisdictional statutes unless diversity)**:
35 U.S.C. sec. 200 et seq.

Brief description of cause:
Unreasonable use and non-use of a publicly funded invention

VII. REQUESTED IN COMPLAINT:

☑ CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ☑ Yes ☐ No

VIII. RELATED CASE(S) IF ANY

(See instructions): JUDGE _____ DOCKET NUMBER _____

DATE March 9, 2011

SIGNATURE OF ATTORNEY OF RECORD

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

JS 44AREVISED June, 2009
IN THE UNITED STATES DISTRICT COURT FOR THE WESTERN DISTRICT OF PENNSYLVANIA
THIS CASE DESIGNATION SHEET MUST BE COMPLETED

PART A

This case belongs on the (○ Erie ○ Johnstown ◉ Pittsburgh) calendar.

1. **ERIE CALENDAR** - If cause of action arose in the counties of Crawford, Elk, Erie, Forest, McKean. Venang or Warren, OR any plaintiff or defendant resides in one of said counties.

2. **JOHNSTOWN CALENDAR** - If cause of action arose in the counties of Bedford, Blair, Cambria, Clearfield or Somerset OR any plaintiff or defendant resides in one of said counties.

3. Complete if on **ERIE CALENDAR**: I certify that the cause of action arose in_____ County and that the _____resides in_____County.

4. Complete if on **JOHNSTOWN CALENDAR**: I certify that the cause of action arose in _____County and that the_____resides in _____County.

PART B (You are to check ONE of the following)

1. ○ This case is related to Number_____ . Short Caption_____
2. ◉ This case is not related to a pending or terminated case.

DEFINITIONS OF RELATED CASES:

CIVIL: Civil cases are deemed related when a case filed relates to property included in another suit or involves the same issues of fact or it grows out of the same transactions as another suit or involves the validity or infringement of a patent involved in another suit EMINENT DOMAIN: Cases in contiguous closely located groups and in common ownership groups which will lend themselves to consolidation for trial shall be deemed related.

HABEAS CORPUS & CIVIL RIGHTS: All habeas corpus petitions filed by the same individual shall be deemed related. All pro se Civil Rights actions by the same individual shall be deemed related.

PARTC

I. CIVIL CATEGORY (Place x in only applicable category).

1. ○ Antitrust and Securities Act Cases
2. ○ Labor-Management Relations
3. ○ Habeas corpus
4. ○ Civil Rights
5. ○ Patent, Copyright, and Trademark
6. ○ Eminent Domain
7. ◉ All other federal question cases
8. ○ All personal and property damage tort cases, including maritime, FELA, Jones Act, Motor vehicle, products liability, assault, defamation, malicious prosecution, and false arrest
9. ○ Insurance indemnity, contract and other diversity cases.
10. ○ Government Collection Cases (shall include HEW Student Loans (Education), V A Overpayment, Overpayment of Social Security, Enlistment Overpayment (Army, Navy, etc.), HUD Loans, GAO Loans (Misc. Types), Mortgage Foreclosures, SBA Loans, Civil Penalties and Coal Mine Penalty and Reclamation Fees.)

I certify that to the best of my knowledge the entries on this Case Designation Sheet are true and correct

Date: March 9, 2011 _____

ATTORNEY AT LAW

NOTE: ALL SECTIONS OF BOTH SIDES MUST BE COMPLETED BEFORE CASE CAN BE PROCESSED.

AO 440 (Rev. 12/09) Summons in a Civil Action

UNITED STATES DISTRICT COURT

for the

Western District of Pennsylvania

Hochendoner, Anita, et al.

Plaintiff

v.

Genzyme Corporation, et al.

Defendant

Civil Action No.

SUMMONS IN A CIVIL ACTION

To: *(Defendant's name and address)* Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142

A lawsuit has been filed against you.

Within 21 days after service of this summons on you (not counting the day you received it) — or 60 days if you are the United States or a United States agency, or an officer or employee of the United States described in Fed. R. Civ. P. 12 (a)(2) or (3) — you must serve on the plaintiff an answer to the attached complaint or a motion under Rule 12 of the Federal Rules of Civil Procedure. The answer or motion must be served on the plaintiff or plaintiff's attorney, whose name and address are:

Matthew L. Kurzweg, Esq.
Kurzweg Law Offices
945 Liberty Avenue
5th Floor Bruno Building
Pittsburgh, PA 15222

If you fail to respond, judgment by default will be entered against you for the relief demanded in the complaint. You also must file your answer or motion with the court.

CLERK OF COURT

Date: _____

_____
Signature of Clerk or Deputy Clerk

Civil Action No.

PROOF OF SERVICE

(This section should not be filed with the court unless required by Fed. R. Civ. P. 4 (l))

This summons for *(name of individual and title, if any)* _____

was received by me on *(date)* _____ .

❒ I personally served the summons on the individual at *(place)* _____

_____ on *(date)* _____ ; or

❒ I left the summons at the individual's residence or usual place of abode with *(name)* _____

_____ , a person of suitable age and discretion who resides there,

on *(date)* _____ , and mailed a copy to the individual's last known address; or

❒ I served the summons on *(name of individual)* _____ , who is

designated by law to accept service of process on behalf of *(name of organization)* _____

_____ on *(date)* _____ ; or

❒ I returned the summons unexecuted because _____ ; or

❒ Other *(specify):*

.

My fees are $ _____ for travel and $ _____ for services, for a total of $ 0.00 .

I declare under penalty of perjury that this information is true.

Date: _____ _____

Server's signature

_____

Printed name and title

_____

Server's address

Additional information regarding attempted service, etc:

AO 440 (Rev. 12/09) Summons in a Civil Action

UNITED STATES DISTRICT COURT

for the

Western District of Pennsylvania

Hochendoner, Anita, et al.

Plaintiff

v.

Genzyme Corporation, et al.

Defendant

Civil Action No.

SUMMONS IN A CIVIL ACTION

To: *(Defendant's name and address)* Mount Sinai School of Medicine of the City University of New York
One Gustave L. Levy Place
New York, NY 10029-6574

A lawsuit has been filed against you.

Within 21 days after service of this summons on you (not counting the day you received it) — or 60 days if you are the United States or a United States agency, or an officer or employee of the United States described in Fed. R. Civ. P. 12 (a)(2) or (3) — you must serve on the plaintiff an answer to the attached complaint or a motion under Rule 12 of the Federal Rules of Civil Procedure. The answer or motion must be served on the plaintiff or plaintiff's attorney, whose name and address are:

Matthew L. Kurzweg, Esq.
Kurzweg Law Offices
945 Liberty Avenue
5th Floor Bruno Building
Pittsburgh, PA 15222

If you fail to respond, judgment by default will be entered against you for the relief demanded in the complaint. You also must file your answer or motion with the court.

CLERK OF COURT

Date: _____

_____
Signature of Clerk or Deputy Clerk

Civil Action No.

PROOF OF SERVICE

(This section should not be filed with the court unless required by Fed. R. Civ. P. 4 (l))

This summons for *(name of individual and title, if any)* _____

was received by me on *(date)* _____ .

❒ I personally served the summons on the individual at *(place)* _____

_____ on *(date)* _____ ; or

❒ I left the summons at the individual's residence or usual place of abode with *(name)* _____

_____ , a person of suitable age and discretion who resides there,

on *(date)* _____ , and mailed a copy to the individual's last known address; or

❒ I served the summons on *(name of individual)* _____ , who is

designated by law to accept service of process on behalf of *(name of organization)* _____

_____ on *(date)* _____ ; or

❒ I returned the summons unexecuted because _____ ; or

❒ Other *(specify):*

.

My fees are $ _____ for travel and $ _____ for services, for a total of $ 0.00 .

I declare under penalty of perjury that this information is true.

Date: _____ _____

Server's signature

_____

Printed name and title

_____

Server's address

Additional information regarding attempted service, etc: