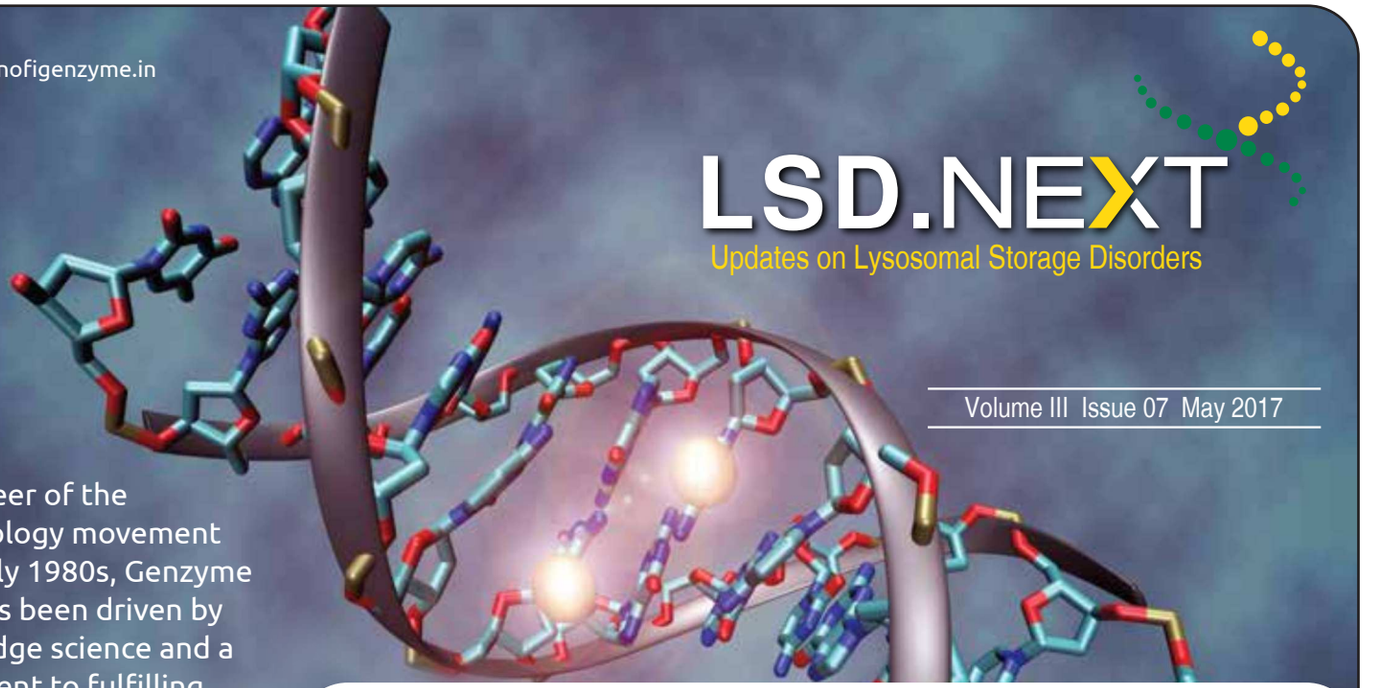
www.sanofigenzyme.in



LSD.NEXT

Updates on Lysosomal Storage Disorders

Volume III Issue 07 May 2017

As a pioneer of the biotechnology movement in the early 1980s, Genzyme has always been driven by cutting-edge science and a commitment to fulfilling unmet medical needs. We have long been known for our expertise in lysosomal storage disorders (LSDs), and continue our focus on R&D related to this area. Our newsletter **LSD.NEXT** is an endeavor to highlight the ongoing research in this niche domain, and we hope that you find this useful.

Shashank
GAUCHER DISEASE

Shashank was diagnosed with Gaucher disease at the age of 14 years and started his treatment in 2006. Shashank, the brave heart, never gave up in life even though he was physically drained and his immunity was severely compromised due to Gaucher Disease. He is doing well now and having completed his MBA degree, he now supports his father in business and strives to be an entrepreneur.

What's in store?

GAUCHER DISEASE

Cerezyme imiglucerase

Long-term hematological, visceral, and growth outcomes in children with Gaucher disease type 3 treated with imiglucerase in the International Collaborative Gaucher Group Gaucher Registry

El-Beshlawy A, Tylki-Szymanska A, Vellodi A, Belmatoug N, Grabowski GA, Kolodny EH, Batista JL, Cox GF, Mistry PK

Mol Genet Metab. 2017 Jan-Feb;120(1-2):47-56

ABSTRACT: In Gaucher disease (GD), deficiency of lysosomal acid β-glucosidase results in a broad phenotypic spectrum that is classified into three types based on the absence (type 1 [GD1]) or presence and severity of primary central nervous system involvement (type 2 [GD2], the fulminant neuronopathic form, and type 3 [GD3], the milder chronic neuronopathic form). Enzyme replacement therapy (ERT) with imiglucerase ameliorates and prevents hematological and visceral manifestations in GD1, but data in GD3 are limited to small, single-center series. The effects of imiglucerase ERT on hematological, visceral and growth outcomes (note: ERT is not expected to directly impact neurologic outcomes) were evaluated during the first 5 years of treatment in 253 children and adolescents (<18years of age) with GD3 enrolled in the International Collaborative Gaucher Group (ICGG) Gaucher Registry. The vast majority of GBA mutations in this diverse global population consisted of only 2 mutations: L444P (77%) and D409H (7%). At baseline, GD3 patients exhibited early onset of severe hematological and visceral disease and growth failure. During the first year of imiglucerase treatment, hemoglobin levels and platelet counts increased and liver and spleen volumes decreased, leading to marked decreases in the number of patients with moderate or severe anemia, thrombocytopenia, and hepatosplenomegaly. These improvements were maintained through Year 5. There was also acceleration in linear growth as evidenced by increasing height Z-scores. Despite devastating disease at baseline, the probability of surviving for at least 5years after starting imiglucerase was 92%.

CONCLUSION: In this large, multinational cohort of pediatric GD3 patients, imiglucerase ERT provided a life-saving and life-prolonging benefit for patients with GD3, suggesting that, with proper treatment, many such severely affected patients can lead productive lives and contribute to society.

http://www.ncbi.nlm.nih.gov/pubmed/28040394

Coming up

Sixteenth ICMR Course in Medical Genetics & Genetic Counseling: 'PEDIGREE TO GENOME'

24th July – 5th August, 2017

- Basic, clinical, molecular genetics simplified.
- Genetic counseling and prenatal diagnosis - Demystified.
- Exposure to common and rare genetic clinical scenarios.
- For details and application form, see - *http://www.sgpgi.ac.in/conf/genetics_ICMR_16_Cpurse_2017.pdf*

- **4th Annual Conference of Society of Indian Academy of Medical Genetics (SIAMG)**

8th – 10th December, 2017

Venue: Thiruvananthapuram, India

INTERNATIONAL CONFERENCES

- **2nd World Congress on Molecular Genetics and Gene Therapy**

03rd – 05th July, 2017

Venue: Bangkok, Thailand

- **Human Genetics Society of Australasia 41st Annual Scientific Meeting 2017**

5th – 8th August, 2017

Venue: South Brisbane, Queensland, Australia

- **13th International Congress of Inborn Errors of Metabolism**

5th – 8th September, 2017

Venue: Rio de Janeiro, Brazil

- **2nd World Congress on Human Genetics**

14th – 15th September, 2017

Venue: Edinburgh, Scotland

- **Human Proteome Organisation 16th Annual World Congress 2017**

17th – 21st September, 2017

Venue: Dublin, Ireland

- **Dutch Society for Human Genetics Autumn Meeting 2017**

21st – 22nd September, 2017

Venue: Koningshof, Netherlands

POMPE DISEASE

Myozyme™ (alglucosidase alfa)

Quantification of muscle pathology in infantile Pompe disease

Schänzer A, Kaiser AK, Mühlfeld C, Kulessa M, Paulus W, von Pein H, Rohrbach M, Viergutz L, Mengel E, Marquardt T, Neubauer B, Acker T, Hahn A

Neuromuscul Disord. 2017 Feb;27(2):141-152

ABSTRACT: The effects of enzyme replacement therapy (ERT) in infantile Pompe disease are variable, necessitating the identification of biomarkers to assess the severity of disease and response to ERT. The aims of this study were to investigate whether quantification of muscle pathology in infantile Pompe disease prior to and during ERT is feasible at the light microscope, and to develop a score that summarizes the degree of muscle pathology in a comprehensive manner from PAS-stained resin sections alone. We, therefore, determined glycogen load, extent of muscle fibre disruption, and amount of autophagic vacuoles in resin-embedded muscle biopsy specimens from 11 infantile Pompe patients and 2 with early childhood phenotype by quantitative methods, correlated the findings with ultrastructural analyses, compared PAS-stained resin sections with conventional PAS-stained cryosections, and related the quantified degree of muscle damage from infantile patients to the effects of ERT. Comparison of electron and light microscopic findings demonstrated that important alterations of skeletal muscle morphology can also be depicted by examining PAS stained resin sections. Infantile patients with good response to ERT had lower muscle pathology score values prior to and during ERT than those with moderate and poor response, but the number of tissue samples available for evaluation was limited.

CONCLUSION: The findings suggest that quantification of muscle pathology by analysing PAS stained resin sections is in principle feasible and useful to monitor disease progression and therapy response. These results have to be validated by investigating a larger group of patients.

http://www.ncbi.nlm.nih.gov/pubmed/27927596

MPS I DISEASE

(Mucopolysaccharidosis Type I)

ALDURAZYME® (LARONIDASE)

Mortality after hematopoietic stem cell transplantation for severe mucopolysaccharidosis type I: the 30-year University of Minnesota experience

Rodgers NJ, Kaizer AM, Miller WP, Rudser KD, Orchard PJ, Braunlin EA

J Inherit Metab Dis. 2017 Mar;40(2):271-280

BACKGROUND AND AIM: Mucopolysaccharidosis IH (MPS IH, Hurler syndrome) naturally leads to death within the first decade of life, primarily from cardiac and pulmonary causes. To determine how hematopoietic stem cell transplantation (HSCT) has altered mortality, we analyzed our institution's 30-year experience of patients with MPS IH undergoing HSCT.

METHODS: Using chart review and the National Death Index, we determined survival status of 134 patients (males = 69) with MPS IH transplanted between 9/16/1983 and 7/25/2013 on 12/31/2013. Analysis included descriptive statistics, Kaplan-Meier curves, and regression analysis by Cox proportional hazards model.

RESULTS: Overall survival (95% CI) at one- and 25-years was 70% (62-78%) and 37% (19-55%), respectively. From 2004 onward, overall survival at one- and 8-years was 84% (73-96%) and 81% (69-94%), respectively, compared to 65% (55-74%) and 57% (47-67%) prior to 2004 (Log-rank p=0.032). Regardless of era, male survival was significantly better than female (HR 0.40, [95% CI: 0.21-0.74], p=0.004). The cumulative incidence of death (95% CI) at 25 years was 63% (45-81%); incidence of pulmonary-related death was the highest at 27% (10-41%) compared to 8% (0.3-16%) for cardiac, 12% (6-17%) for infectious disease, and 16% (3-27%) from other complications.

CONCLUSIONS: HSCT has increased survival in MPS IH beyond the third decade of life and decreased the incidence of cardiac mortality, but deaths after the third year post-HSCT occur in excess of

expected US mortality. It is important to determine if improved transplant strategies since 2004 result in better long-term survival in the current patient population.

http://www.ncbi.nlm.nih.gov/pubmed/28054207

FABRY DISEASE

Right Ventricular Hypertrophy, Systolic Function, and Disease Severity in Anderson-Fabry Disease: An Echocardiographic Study

Graziani F, Laurito M, Pieroni M, Pennestrì F, Lanza GA, Coluccia V, Camporeale A, Pedicino D, Verrecchia E, Manna R, Crea F

J Am Soc Echocardiogr. 2017 Mar;30(3):282-291

BACKGROUND: Right ventricular (RV) involvement has been described in Anderson-Fabry disease (AFD), especially in patients with established Fabry cardiomyopathy (FC). However, few and controversial data on RV systolic function are available, and there are no specific tissue Doppler studies.

METHODS: Detailed echocardiographic examinations were performed in 45 patients with AFD. FC, defined as maximal left ventricular wall thickness ≥15 mm, was present in 12. The Mainz Severity Score Index was calculated for each patient. Pulsed tissue Doppler was applied to the RV free wall at the tricuspid annular level and at the septal and lateral corners at the mitral annular level to obtain systolic tissue Doppler velocities (RV Sa, septal Sa, and lateral Sa, respectively). Twelve patients with amyloid light-chain cardiac amyloidosis were studied as a control group.

RESULTS: Echocardiography revealed RV hypertrophy (RVH) in 31% of patients with AFD, all but one of whom were male and all of whom had concomitant left ventricular hypertrophy (LVH). All patients with AFD had normal RV fractional area change (47.9 ± 6.5%) and tricuspid annular plane systolic excursion (21.7 ± 3.2 mm) and all but one also had normal RV Sa (13.2 ± 2.2 cm/sec). RVH positively correlated with indices of LVH (r = 0.8, P = .0001, for all parameters evaluated), as well as with Mainz Severity Score Index (r = 0.70, P = .0001). Septal and lateral Sa were decreased in almost all patients (means, 7.7 ± 1.8 and 7.9 ± 1.9 cm/sec, respectively), irrespective of the presence of LVH. Compared with control subjects with cardiac amyloidosis, patients with FC showed better indices of RV systolic function (P < .001 for all: tricuspid annular plane systolic excursion, RV fractional area change, and RV Sa) despite similar RV wall thickness (6.2 ± 1.2 vs 6.9 ± 1.9 mm, P = NS).

CONCLUSIONS: RVH is common in patients with AFD and correlates with disease severity and LVH. RVH, however, does not significantly affect RV systolic function. Patients with FC have better RV systolic function compared with those with cardiac amyloidosis with similar levels of RV thickness. The combination of low LV Sa values and normal RV Sa values might be helpful in the differential diagnosis of infiltrative heart disease.

http://www.ncbi.nlm.nih.gov/pubmed/28069318

ASMD DISEASE TYPES A AND B

(Acid sphingomyelinase deficiency Types A and B)

Quantitation of plasmatic lysosphingomyelin and lysosphingomyelin-509 for differential screening of Niemann-Pick A/B and C diseases

Kuchar L, Sikora J, Gulinello ME, Poupetova H, Lugowska A, Malinova V, Jahnova H, Asfaw B, Ledvinova J

Anal Biochem. 2017 Mar 1;525:73-77

ABSTRACT: Acid sphingomyelinase deficiency (ASMd, Niemann-Pick disease A/B) and Niemann-Pick type C disease (NPC) share core clinical symptoms. Initial diagnostic discrimination of these two rare lysosomal storage diseases is thus difficult. As sphingomyelin accumulates in ASMd as well as NPC, lysosphingomyelin (sphingosylphosphorylcholine) and its m/z 509 analog were suggested as biomarkers for both diseases.

CONCLUSION: Herein we present re-

Society for Indian Academy of Medical Genetics

SANOFI GENZYME

SIAMG-GENZYME FELLOWSHIP IN CLINICAL GENETICS

Applications invited for 3-month fellowship program.

Sanofi Genzyme, in association with Society for Indian Academy of Medical Genetics (SIAMG), launched a fellowship programme in the field of medical genetics in 2013. This 3-month fellowship programme is currently offered at 7 premier institutes across India:
AIIMS – Delhi, SGRH – Delhi, SGPGI – Lucknow, NIMS – Hyderabad, CMC – Vellore, KMC - Manipal and SAT - Thiruvanthapuram.
These premier institutes offer the clinical expertise as well as diagnostic infrastructure and capabilities in the area of clinical genetics to program participants to learn and observe.

The fellowship is open to post graduate degree holders or final year students of MD/MS/DNB or an equivalent degree holder in Pediatrics, Internal Medicine or Obstetrics & Gynecology specialty, recognized by the Medical Council of India. Medical professionals with super-specialization (DM) can also apply for the course. Qualified applicants will be screened by the committee established by SIAMG, to select participants for the fellowship programme. Application forms can be downloaded from *www.iamg.in* or can be requested through *email: info@iamg.in*

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lsd.next@genzyme.com

sults of simultaneous LC-ESI-MS/MS measurements of lysosphingomyelin and lysosphingomyelin 509 in plasma and dried blood spots (DBS) collected from ASMd and NPC patients and suggest that the plasma but not DBS levels of the two analytes allow differential biochemical screening of ASMd and NPC.
http://www.ncbi.nlm.nih.gov/pubmed/28259515

SOUTH ASIA FORUM

Inherited Metabolic Disorders: Efficacy of Enzyme Assays on Dried Blood Spots for the Diagnosis of Lysosomal Storage Disorders

Verma J, Thomas DC, Kasper DC, Sharma S, Puri R, Bijarnia-Mahay S, Mistry PK, Verma IC

JIMD Rep. 2017;31:15-27

ABSTRACT: High consanguinity rates, poor access to accurate diagnostic tests, and costly therapies are the main causes of increased burden of lysosomal storage disorders (LSDs) in developing countries. Therefore, there is a major unmet need for accurate and economical diagnostic tests to facilitate diagnosis and consideration of therapies before irreversible complications occur. In cross-country study, we utilized dried blood spots (DBS) of 1,033 patients clinically suspected to harbor LSDs for enzymatic diagnosis using modified fluorometric assays from March 2013 through May 2015. Results were validated by demonstrating reproducibility, testing in different sample types (leukocytes/plasma/skin fibroblast), mutation study, or measuring specific biomarkers. Thirty percent (307/1,033) were confirmed to have one of the LSDs tested. Reference intervals established unambiguously identified affected patients. Correlation of DBS results with other biological samples (n=172) and mutation studies (n=74) demonstrated 100% concordance in Gaucher, Fabry, Tay Sachs, Sandhoff, Niemann-Pick, GM1, Neuronal ceroid lipofuscinosis (NCL), Fucosidosis, Mannosidosis, Mucopolysaccharidosis (MPS) II, IIIb, IVa, VI, VII, and I-Cell diseases, and 91.4% and 88% concordance in Pompe and MPS-I, respectively. Gaucher and Pompe are the most common LSDs in India and Pakistan, followed by MPS-I in both India and Sri Lanka. Study demonstrates utility of DBS for reliable diagnosis of LSDs. Diagnostic accuracy (97.6%) confirms veracity of enzyme assays. Adoption of DBS will overcome significant hurdles in blood sample transportation from remote regions. DBS enzymatic and molecular diagnosis should become the standard of care for LSDs to make timely diagnosis, develop personalized treatment/monitoring plan, and facilitate genetic counseling.

KEYWORDS: Diagnostic accuracy; Dried blood spots; Enzymatic diagnosis; Lysosomal enzymes; Lysosomal storage disorders; Molecular diagnosis.

http://www.ncbi.nlm.nih.gov/pubmed/27008195

Knowledge Forum

1. Fabry disease and primary erythromelalgia share similar symptoms, therefore, it is a good strategy for clinical physicians to perform genetic mutation screenings on both SCN9A and GLA genes in those patients with limb burning pain but without a clear inheritant pattern.
   https://www.ncbi.nlm.nih.gov/pubmed/27211852
2. Enzyme replacement therapy with laronidase can be used pre- and peri-haemopoietic stem cell transplantation, which is the gold standard treatment in patients diagnosed less than 2.5 years of age.
   https://www.ncbi.nlm.nih.gov/pubmed/27033167
3. Lysosomal acid lipase deficiency (LAL-D) should be incorporated into the differential diagnosis in relevant clinical settings where other diseases, such as Gaucher disease and Niemann-Pick disease, are initially suspected.
   https://www.ncbi.nlm.nih.gov/pubmed/27876313

GZIN.XLSD.17.05.0024

SANOFI GENZYME

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For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

ABRIDGED PRESCRIBING INFORMATION

Cerezyme® Injection400 Units

Imiglucerase Powder for Concentrate for Solution for Infusion

COMPOSITION: Each vial contains Cerezyme 400 U of imiglucerase and the following excipients: mannitol, sodium citrate, citric acid monohydrate and polysorbate 80.

THERAPEUTIC INDICATION: Cerezyme® (imiglucerase for injection) is indicated for use as long-term enzyme replacement therapy in patients with a confirmed diagnosis of non-neuronopathic (Type 1) or chronic neuronopathic (Type 3) Gaucher disease who exhibit clinically significant non-neurological manifestations of the disease.

DOSAGE & ADMINISTRATION: Therapy should be directed by physicians knowledgeable in the management of Gaucher disease. Initial doses of 60 U/kg of body weight once every 2 weeks have shown improvement in haematological and visceral parameters within 6 months of therapy and continued use has either stopped progression of or improved bone disease. Administration of doses as low as 2.5 U/kg of body weight three times a week or 15 U/kg of body weight once every 2 weeks has been shown to improve haematological parameters and organomegaly, but not bone parameters. The reconstituted and diluted preparation is administered by intravenous infusion over 1 to 2 hours. Infusion of Cerezyme at home may be considered for patients who are tolerating their infusions well for several months. Decision to have patient move to home infusion should be made after evaluation and recommendation by the treating physician.

SAFETY RELATED INFORMATION:

Contraindications: Hypersensitivity to the active substance or to any of the excipients.

Warnings & Precautions:

Hypersensitivity/Anaphylactic reactions: As with any intravenous protein product, severe allergic-type hypersensitivity reactions are possible, but occur uncommonly. If these reactions occur, immediate discontinuation of the Cerezyme infusion is recommended and appropriate medical treatment should be initiated. The current medical standards for emergency treatment of anaphylactic reactions are to be observed. Patients with antibody to imiglucerase have a higher risk of hypersensitivity reactions.

Infusion Associated Reactions: Patients may develop infusion associated reactions (IARs). IARs are defined as any related adverse event occurring during the infusion or during the hours following infusion.

Pregnancy: Limited experience from 150 pregnancy outcomes (primarily based on spontaneous reporting and literature review) is available suggesting that use of Cerezyme is beneficial to control the underlying Gaucher disease in pregnancy. Furthermore, these data indicate no malformative toxicity for the foetus by Cerezyme, although the statistical evidence is low. Treatment naïve women should be advised to consider commencing therapy prior to conception in order to attain optimal health. In women receiving Cerezyme treatment continuation throughout pregnancy should be considered.

Lactation: It is not known whether this active substance is excreted in human milk, however, the enzyme is likely to be digested in the child's gastrointestinal tract.

ADVERSE REACTIONS: Most common adverse drug reactions are – Dyspnoea, Coughing, Hypersensitivity reactions, urticaria/angioedema, pruritus and rash.

For full prescribing information please contact: Sanofi Genzyme, 1st Floor, Technopolis, Golf Course Road, Sector 54, Gurgaon – 122 001, India.

Source: Cerezyme India Prescribing Information dated September 2014
Date: January 2017

MYOZYME®

Alglucosidase alfa 50mg power for concentrate for solution for infusion

COMPOSITION: Each vial contains alglucosidase alfa 50 mg lyophilized powder for concentrate for solution for infusion). After reconstitution, the solution contains 5 mg of alglucosidase alfa per ml and after dilution, the concentration varies from 0.5 mg to 4 mg/ml.
Alglucosidase alfa is a recombinant form of human acid α-glucosidase and is produced in Chinese hamster ovary cells (CHO) by recombinant DNA technology.

THERAPEUTIC INDICATION: Myozyme is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid -glucosidase deficiency).

DOSAGE & ADMINISTRATION: The recommended dose regimen of alglucosidase alfa is 20 mg/kg of body weight administered as intravenous infusion once every 2 weeks. Myozyme has to be reconstituted with water for injections, then diluted with sodium chloride 9 mg/ml (0.9%) solution for injection and then administered by intravenous infusion using aseptic techniques. A 0.2 micron low protein binding in-line filter should be used for administration. Infusions should be administered incrementally. It is recommended that the infusion begin at an initial rate of 1 mg/kg/h and be gradually increased by 2 mg/kg/h every 30 minutes if there are no signs of infusion associated reactions (IARs) until a maximum rate of 7 mg/kg/h is reached.

SAFETY RELATED INFORMATION:

Contraindications: Life threatening hypersensitivity (anaphylactic reaction) to the active substance or to any of the excipients, when rechallenge was unsuccessful.

Warnings & Precautions:

Hypersensitivity/Anaphylactic reactions: Serious and life-threatening anaphylactic reactions, including anaphylactic shock, have been reported in infantile- and late-onset patients during Myozyme infusions. The current medical standards for emergency treatment of anaphylactic reactions are to be observed.

Infusion Associated Reactions: Patients may develop infusion associated reactions (IARs). IARs are defined as any related adverse event occurring during the infusion or during the hours following infusion. Patients with an acute illness (e.g. pneumonia, sepsis) at the time of Myozyme infusion appear to be at greater risk for IARs.

Immunogenicity: Patients who experience hypersensitivity reactions may also be tested for IgE antibodies to alglucosidase alfa and other mediators of anaphylaxis. Patients who develop IgE antibodies to alglucosidase alfa appear to be at a higher risk for the occurrence of IARs when Myozyme is re-administered.

Immune-mediated reactions: Patients should be monitored for signs and symptoms of systemic immune-mediated reactions involving skin and other organs while receiving alglucosidase alfa.

Immunomodulation: Patients with Pompe disease are at risk of respiratory infections due to the progressive effects of the disease on the respiratory muscles. Therefore, treating patients with Pompe disease with immunosuppressive agents may further increase the risk of developing severe respiratory infections and vigilance is recommended.

Pregnancy: Myozyme should not be used during pregnancy unless clearly necessary.

Lactation: Alglucosidase alfa may be excreted in breast milk. Because there are no data available on effects in neonates exposed to alglucosidase alfa via breast milk, it is recommended to stop breast-feeding when Myozyme is used.

ADVERSE REACTIONS: Hypersensitivity, Agitation, Tremor, Dizziness, Paraesthesia, Headache, Tachycardia, Cyanosis, Flushing, Hypertension, Pallor, Cough, Throat tightness, Vomiting, Retching, Nausea, Diarrhoea, Urticaria, Rash, Erythema, Rash maculopapular, Rash macular, Rash popular, Pruritus, Hyperhidrosis, Muscle spasms, Muscle twitching, Myalgia, Pyrexia, Irritability, Chills, Chest discomfort, Peripheral oedema, Local swelling, Fatigue, Feeling hot, Chest pain, Face edema, Peripheral coldness, Infusion site pain, Infusion site reaction, Oxygen saturation decreased, Heart rate increased, Blood pressure increased, Body temperature increased.

For full prescribing information please contact: Sanofi Genzyme, 1st Floor, Technopolis, Golf Course Road, Sector 54, Gurgaon – 122 001, India.

Source: Myozyme India Prescribing Information dated September 2014
Date: June 2016

ALDURAZYME® (LARONIDASE)

Solution for Intravenous Infusion Only

COMPOSITION: ALDURAZYME, for intravenous (IV) infusion, is supplied as a sterile, single-use, colorless solution in a 5ml glass vial containing 2.9 mg laronidase, 43.9 mg sodium chloride, 63.5 mg sodium phosphate monobasic monohydrate, 10.7 mg sodium phosphate dibasic heptahydrate, and 0.05 mg polysorbate 80.

THERAPEUTIC INDICATION: ALDURAZYME (laronidase) is indicated for patients with Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I (MPS I) and for patients with the Scheie form who have moderate to severe symptoms.

DOSAGE AND ADMINISTRATION: Each vial of ALDURAZYME is intended for single use only. The recommended dosage regimen of is 0.58 mg/kg of body weight administered once weekly as an intravenous (IV) infusion. Pretreatment is recommended 60 minutes prior to the start of the infusion and may include antihistamines, antipyretics, or both. The concentrated solution for infusion must be diluted with 0.9% Sodium Chloride Injection, USP, to a final volume of 100 mL or 250 mL, using aseptic techniques. The final volume of the infusion is determined by the patient's body weight. Patients with a body weight of 20 kg or less should receive a total volume of 100 mL. Patients with a body weight greater than 20 kg should receive a total volume of 250 mL.The entire infusion volume (100 mL for patients weighing 20 kg or less and 250 mL for patients weighing greater than 20 kg) should be delivered over approximately 3 to 4 hours.

SAFETY RELATED INFORMATION:

Contraindications: None.

Warnings and precautions:

Anaphylaxis and Allergic Reactions: Anaphylaxis and severe allergic reactions have been observed in patients during or up to 3 hours after ALDURAZYME infusions.

Acute Respiratory Complications Associated with Administration: Patients with an acute febrile or respiratory illness at the time of ALDURAZYME infusion may be at greater risk for infusion reactions. Evaluation of airway patency should be considered prior to initiation of treatment with ALDURAZYME.

Risk of Acute Cardiorespiratory Failure: Caution should be exercised when administering ALDURAZYME to patients susceptible to fluid overload or patients with acute underlying respiratory illness or compromised cardiac and/or respiratory function for whom fluid restriction is indicated.

Infusion Reactions: Because of the potential for infusion reactions, patients should receive antipyretics and/or antihistamines prior to infusion.

USE IN SPECIFIC POPULATIONS:

Pregnancy: There are no adequate and well-controlled studies of ALDURAZYME in pregnant women. Aldurazyme should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether the drug is excreted in human milk. Caution should be exercised when ALDURAZYME is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of ALDURAZYME in patients with MPS I, ages 6 months to 5 years old, was found to be similar to the safety and effectiveness of ALDURAZYME in pediatric patients 6 to 18 years and adults.

ADVERSE REACTIONS: The most common adverse reactions with ALDURAZYME were infusion reactions e.g. flushing, pyrexia, headache, and rash. Other reported adverse reactions included bronchospasm, dyspnea, urticaria and pruritus.

Immunogenicity: Potential for antibody neutralization of cellular uptake has not been assessed. As with all the therapeutic proteins, there is potential for immunogenicity.

For full prescribing information please contact: Sanofi Genzyme, 1st Floor, Technopolis, Golf Course Road, Sector 54, Gurgaon – 122 001, India.

Source: Aldurazyme India Prescribing Information
Date: July 2016

FABRAZYME®

Fabrazyme® 35mg powder for concentrate for solution for intravenous infusion

COMPOSITION: Each vial of Fabrazyme contains a nominal value of 35 mg of agalsidase beta. After reconstitution with 7.2 ml water for injections, each vial of Fabrazyme contains 5 mg/ml (35 mg/7 ml) of agalsidase beta. The reconstituted solution must be diluted further.
Agalsidase beta is a recombinant form of human α-galactosidase A and is produced by recombinant DNA technology using a mammalian Chinese Hamster Ovary (CHO) cell culture.

THERAPEUTIC INDICATION: Fabrazyme is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency).

DOSAGE & ADMINISTRATION: The recommended dosage of Fabrazyme is 1 mg/kg body weight infused every 2 weeks as an IV infusion. No dose adjustment is necessary for patients with renal insufficiency.
Patients should receive antipyretics prior to infusion. In clinical trials, the initial IV infusion rate should be no more than 0.25 mg/min or 15 mg/hr. The infusion rate may be slowed in the event of infusion reactions. After patient tolerance has been established, the infusion rate may be increased gradually with subsequent infusions, as tolerated.
Reconstitute each 35 mg vial of Fabrazyme by slowly injecting 7.2 mL of Sterile Water for Injection. Fabrazyme should be diluted in sodium chloride 9 mg/mL (0.9%) solution for infusion immediately after reconstitution, to a final concentration between 0.05 mg/mL and 0.7 mg/mL. The diluted solution may be filtered through an in-line, low protein-binding 0.2 µm filter during administration. Store Fabrazyme under refrigeration between 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.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).

SAFETY RELATED INFORMATION:

Contraindications: Life threatening hypersensitivity (anaphylactic reaction) to the active substance or any of the excipients listed

Warnings & Precautions:

Hypersensitivity/Anaphylactic reactions: As with any intravenous protein medicinal product, allergic-type hypersensitivity reactions are possible. A small number of patients have experienced reactions suggestive of immediate (Type I) hypersensitivity. If severe allergic or anaphylactic-type reactions occur, immediate discontinuation of the administration of Fabrazyme should be considered and appropriate treatment initiated. The current medical standards for emergency treatment are to be observed. With careful rechallenge Fabrazyme has been re-administered to all 6 patients who tested positive for IgE antibodies or had a positive skin test to Fabrazyme in a clinical trial. In this trial, the initial rechallenge administration was at a low dose and a lower infusion rate (the therapeutic dose at the initial standard recommended rate). Once a patient tolerates the infusion, the dose may be increased to reach the therapeutic dose of 1 mg/kg and the infusion rate may be increased by slowly titrating upwards, as tolerated.

Infusion Associated Reactions: Patients with antibodies to r-hαGAL have a greater potential to experience infusion-associated reactions (IARs), which are defined as any related adverse event occurring on the infusion day. These patients should be treated with caution when re-administering agalsidase beta. Antibody status should be regularly monitored.
In clinical trials, sixty seven percent (67 %) of the patients experienced at least one infusion-associated reaction. The frequency of IARs decreased over time. Patients experiencing mild or moderate infusion-associated reactions when treated with agalsidase beta during clinical trials have continued therapy after a reduction in the infusion rate (0.15 mg/min; 10 mg/hr) and/or pre-treatment with antihistamines, paracetamol, ibuprofen and/or corticosteroids.

Immunogenicity: Since agalsidase beta (r-hαGAL) is a recombinant protein, the development of IgG antibodies is expected in patients with little or no residual enzyme activity. The majority of patients developed IgG antibodies to r-hαGAL, typically within 3 months of the first infusion with Fabrazyme. Over time, the majority of seropositive patients in clinical trials demonstrated either a downward trend in titers (based on a ≥ 4-fold reduction in titer from the peak measurement to the last measurement) (40% of the patients), tolerised (no detectable antibodies confirmed by 2 consecutive radioimmunoprecipitation (RIP) assays) (14% of the patients) or demonstrated a plateau (35% of the patients).

Paediatric use: Safety and efficacy profile of Fabrazyme treatment in pediatric patients was found to be consistent with that seen in adults. The safety and efficacy in patients younger than 8 years of age have not been evaluated.

Pregnancy: There are no adequate data from the use of agalsidase beta in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to embryonal/foetal development. Fabrazyme should not be used during pregnancy unless clearly necessary.

Lactation: 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.

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.

For full prescribing information please contact: Sanofi Genzyme, 1st Floor, Technopolis, Golf Course Road, Sector 54, Gurgaon – 122 001, India.

Source: Fabrazyme India Prescribing Information dated September 2014
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