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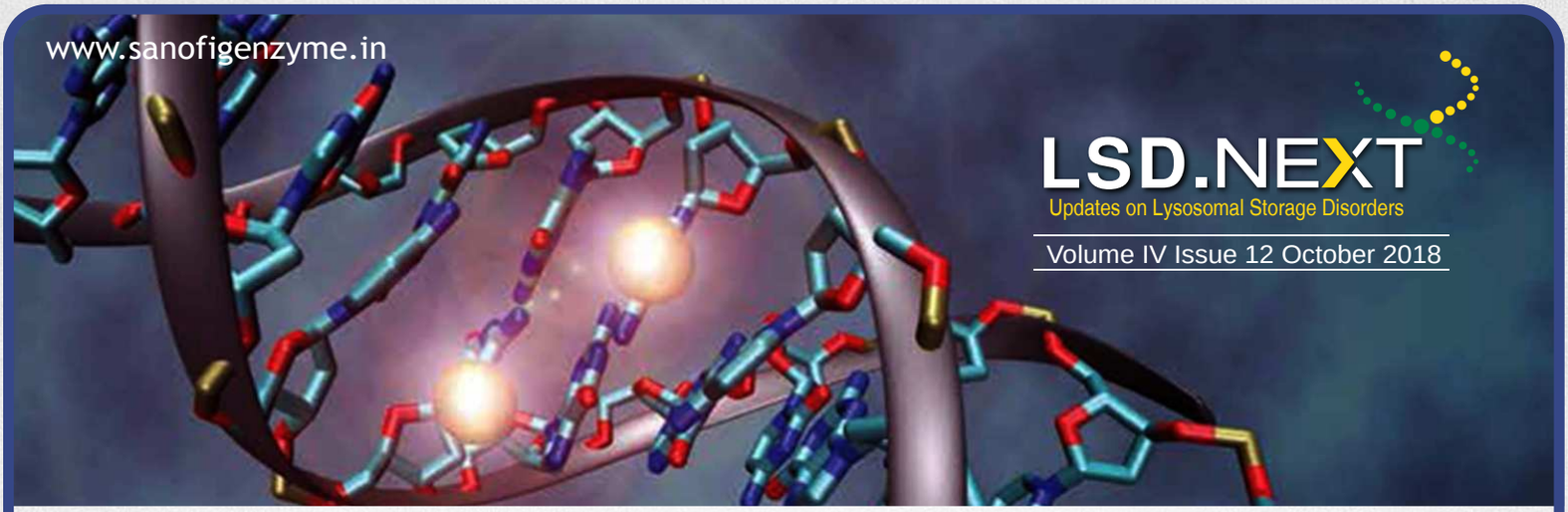
LSD.NEXT
Updates on Lysosomal Storage Disorders

Volume IV Issue 12 October 2018



Key Highlights in this issue

Outcomes after 8 Years of Eliglustat Therapy for Gaucher Disease Type 1: Final Results from the Phase 2 Trial

36-Months follow-up assessment after cessation and resuming of enzyme replacement therapy in late onset Pompe disease: data from the Swiss Pompe Registry

False positive screen test for mucopolysaccharidoses in healthy female newborns

Correlations between Serum Cholesterol and Vascular Lesions in Fabry Disease Patients

Hepatosplenomegaly, pneumopathy, bone changes and fronto-temporal dementia: Niemann-Pick type B and SQSTM1-associated Paget's disease in the same individual

Biochemical and molecular characterization of adult patients with type I Gaucher disease and carrier frequency analysis of Leu444Pro–a common Gaucher disease mutation in India

SANOFI GENZYME

What's in store?

As a pioneer of the biotechnology movement in the early 1980s, Sanofi 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 TYAGI
GAUCHER DISEASE

Shashank use to fall ill quite often as a child, bouts of sickness had become an everyday thing including liver enlargement; his growth was less compared to the other children his age. He was diagnosed with Gaucher's disease at AIIMS and started his treatment in 2006. Shashank is doing well now; he is a young man who has finished his MBA and jointly supporting the family business as well as working closely with Lysosomal Storage Disorders Support Society of India for betterment of patients suffering with LSDs.

Cerezyme® imiglucerase

GAUCHER DISEASE

Outcomes after 8 Years of Eliglustat Therapy for Gaucher Disease Type 1: Final Results from the Phase 2 Trial

Lukina E, Watman N, Dragosky M, Lau H, Arreguin EA, Rosenbaum H, Zimran A, Foster MC, Gaemers SJM, Peterschmitt MJ

Am J Hematol. 2018 Sep 28.
doi: 10.1002/ajh.25300.

ABSTRACT: Eliglustat is a first-line oral therapy for adults with Gaucher disease type 1 (GD1) and poor, intermediate or extensive CYP2D6-metabolizer phenotypes (>90% of patients). We report the final results of a Phase 2 trial and extension (NCT00358150) in previously untreated adult GD1 patients who had splenomegaly with thrombocytopenia and/or anemia and received 50 or 100 mg eliglustat tartrate (equivalent to 42 or 84 mg eliglustat) twice daily for 8 years. Nineteen of 26 patients completed the trial. After 8 years of eliglustat, mean spleen and liver volumes decreased by 69% and 34%, respectively. Mean hemoglobin concentration and platelet count increased by 2.2 g/dL and 113%, respectively. All patients met at least three of four therapeutic goals established for patients on long-term enzyme replacement therapy. Mean final values for patients with severe splenomegaly (n=6), moderate-to-severe anemia (n=6), severe thrombocytopenia (n=8), or osteoporosis (n=6) were similar to patients with milder disease at baseline and within long-term therapeutic goal thresholds. Median chitotriosidase levels decreased by 91%, CCL18 by 87%, glucosylsphingosine by 92%, and plasma glucosylceramide by 80%. Mean lumbar spine T-score increased by 0.96, moving from the osteopenic to the normal range. Mean quality-of-life scores, mostly below normal at baseline, moved into ranges seen in healthy adults. Eliglustat was well-tolerated; 98% of adverse events were mild or moderate and 94% were considered unrelated to treatment. Clinically meaningful improvements in all parameters continued or were maintained over 8 years, with the largest margins of improvement seen in the most severely affected patients.

https://www.ncbi.nlm.nih.gov/pubmed/30264864

Myozyme® (alglucosidase alfa)

POMPE DISEASE

36-Months follow-up assessment after cessation and resuming of enzyme replacement therapy in late onset Pompe disease: data from the Swiss Pompe Registry

Scheidegger O, Leupold D, Sauter R, Findling O, Rösler KM, Hundsberger T

J Neurol. 2018 Sep 19.
doi: 10.1007/s00415-018-9065-7.

INTRODUCTION: Although not curative, enzyme replacement therapy (ERT) with recombinant human acid alpha-glucosidase enzyme has shown to be effective in the treatment of late-onset Pompe disease (LOPD). For this potentially life-long treatment, little is known on the clinical effect of cessation and resuming ERT. Due to a Swiss Supreme Court decision on ERT reimbursement, a temporary stop of ERT occurred in our study population. The aim of this study was to report the 36-months follow-up assessments after resuming ERT.

METHODS: After resuming ERT, seven patients suffering from genetically and enzymatically confirmed LOPD had periodic, mandatory, prospective assessments of pulmonary function tests, muscle strength summary scores, distances walked in timed walking tests, and patient-reported questionnaires. Data were statistically analyzed for significant differences between time points at ERT cessation, at ERT resuming, and 36 months thereafter.

RESULTS: After resuming ERT forced vital capacity (p=0.007) and distance walked in the 6 min walk test (6-MWT, p=0.011) significantly increased at 36 months. Compared to before ERT ces-

Coming up

NATIONAL CONFERENCES

- **4th International Birth Defects Conference & 5th Annual Conference of the Society of Indian Academy of Medical Genetics**

13th – 15th December, 2018

Venue: Christian Medical College, Vellore, Tamil Nadu, India

INTERNATIONAL CONFERENCES

- **American Academy of Pediatrics: 2018 National Conference & Exhibition**

2nd – 6th November, 2018

Venue: Orlando, United States

- **4th International Paediatric Medical Congress 2018**

15th – 17th November, 2018

Venue: Dubai, United Arab Emirates

sation, distance walked in 6-MWT at 36 months still remained significantly lower (p=0.005). Self-reported scores in the fatigue severity scale significantly declined at 36 months after resuming ERT (p=0.019). No other functional or reported parameter significantly changed at 36 months after resuming ERT.

CONCLUSIONS: Our data suggests that long-term interruption of ERT in LOPD may lead to deterioration of clinical meaningful parameters and quality of life. In addition, a clinical restoration after ERT cessation is possible for most of the LOPD patients within a 36 months follow-up.

http://www.ncbi.nlm.nih.gov/pubmed/30232608

MPS I DISEASE

(Mucopolysaccharidosis Type I)

ALDURAZYME® (LARONIDASE)

False positive screen test for mucopolysaccharidoses in healthy female newborns

Monachesi C, Zampini L, Padella L, Marchesiello RL, Galeazzi T, Santoro L, Catassi C, Gasparrini E, Carnielli VP, Volpi N, Fiumara A, Concolino D, Tomanin R, Coppa GV, Gabrielli O

Clin Chim Acta. 2018 Nov;486:221-223. doi: 10.1016/j.cca.2018.08.016.

BACKGROUND: In total, 930 urine samples obtained on 2nd and 3rd day from birth have been analyzed for the early diagnosis of Mucopolysaccharidoses.

METHODS: Dimethylmethylene blue (DMB) assay and one-dimensional electrophoresis were performed in all urine samples. Agarose gel electrophoresis, before and after treatment with chondroitinase ABC and heparinases, was used for a comprehensive characterization.

RESULTS: Out of 930 urine samples 7 showed anomalous electrophoretic pattern; 5 of them had high GAG levels by DMB test. Atypical samples (n=7) were analyzed by agarose gel electrophoresis. After enzymatic digestion, some slow bands were still visible. A second urine sample of the above 7 newborns was analyzed at the age of 1month, demonstrating both a normal pattern and normal GAG levels. Additional urine and vaginal mucus samples from 10 term neonates with vaginal bleeding showed the same electrophoretic pattern observed in the 7 false positive samples.

CONCLUSIONS: The altered electrophoretic pattern may be due to the presence of glycoproteins and not to specific GAGs, due to high levels of maternal hormones exposure during pregnancy. To our knowledge, this is the first time maternal estrogen hormones are proposed as a likely cause of false-positive urinary glycosaminoglycan screen test in healthy newborns.

http://www.ncbi.nlm.nih.gov/pubmed/30110607

FABRY DISEASE

Fabrazyme® agalsidase beta

Correlations between Serum Cholesterol and Vascular Lesions in Fabry Disease Patients

Katsuta H, Tsuboi K, Yamamoto H, Goto H

Circ J. 2018 Oct 3. doi: 10.1253/circj.CJ-18-0378

BACKGROUND: Fabry disease is an X-linked lysosomal storage disorder and shows globotriosylceramide (Gb3) accumulation in multiple organs, resulting from a deficiency of α-galactosidase. In patients with Fabry disease, cardiovascular disease occurs at an early age. Previous studies have shown that serum levels of high-density lipoprotein-cholesterol (HDL-C) increase in this disease, yet its clinical significance for cardiovascular disease remains unclear. MethodsandResults: In order to determine why the serum HDL-cholesterol is high in various cardiovascular diseases of Fabry disease patients, we evaluated the serum lipid profiles, ocular vascular lesions, and levels of serum vascular endothelial growth factor (VEGF) and intercellular adhesion molecule-1 in 69 patients with Fabry disease diagnosed by genetic examination. The serum HDL-C/total cholesterol (T-Chol) ratio was significantly high, especially in male patients (41.5±1.7%) regardless of body

mass index. Ocular vascular lesions were more likely to occur in female patients with a high HDL-C/T-Chol ratio compared with most male patients. Female patients with a high HDL-C/T-Chol ratio also presented a high serum VEGF level, suggesting that vascular endothelium dysfunction and arteriosclerotic changes progress more severely than in patients with a normal HDL-C/T-Chol ratio. In most patients, enzyme replacement therapy improved serum Gb3 and lyso-Gb3 levels, but these Gb3 and lyso-Gb3 still remained higher than in healthy controls, which appears to result in continuous vascular arteriosclerotic changes.

CONCLUSIONS: We concluded that increased low-density lipoprotein-cholesterol uptake to the vascular wall caused by endothelial dysfunction is likely to contribute to the high HDL-C/T-Chol ratio observed in Fabry disease patients

http://www.ncbi.nlm.nih.gov/pubmed/30282881

ASMD DISEASE TYPES A AND B

(Acid sphingomyelinase deficiency Types A and B)

Hepatosplenomegaly, pneumopathy, bone changes and fronto-temporal dementia: Niemann-Pick type B and SQSTM1-associated Paget's disease in the same individual

Voinea C, Gonzalez Rodriguez E, Beigelman-Aubry C, Leroy V, Aubry-Rozier B, Campos-Xavier B, Ballhausen D, Lazor R, Barbey F, Bonafé L, Superti-Furga A, Tran C

J Bone Miner Metab. 2018 Jun 14. doi: 10.1007/s00774-018-0932-1.

ABSTRACT: Data from exome sequencing show that a proportion of individuals in whom a genetic disorder is suspected turn out to have not one, but two to four distinct ones. This may require an evolution in our diagnostic attitude towards individuals with complex disorders. We report a patient with splenomegaly, pneumopathy, bone changes and fronto-temporal dementia (FTD). "Sea-blue histiocytes" in his bone marrow pointed to a lysosomal storage disease. Homozygosity for a pathogenic mutation in the SMPD1 gene confirmed Niemann-Pick disease type B (NPD-B). Mild cognitive impairment and abnormal brain FDG PET were consistent with FTD. We initially tried to fit the skeletal and neurologic phenotype into the NPD-B diagnosis. However, additional studies revealed a pathogenic mutation in the SQSTM1 gene. Thus, our patient had two distinct diseases; NPD-B, and Paget's disease of bone with FTD. The subsequent finding of a mutation in SQSTM1 gene ended our struggle to explain the combination of findings by a singular "unifying" diagnosis and allowed us to make specific therapeutic decisions. SQSTM1 mutations have been reported in association with FTD, possibly because of defective autophagy. Bisphosphonates may be beneficial for PDB, but since they are known to inhibit acid sphingomyelinase activity, we refrained from using them in this patient. While the principle of looking for unifying diagnosis remains valid, physicians should consider the possibility of co-existing multiple diagnoses when clinical features are difficult to explain by a single one. Accurate diagnostic work-up can guide genetic counseling but also lead to better medical management.

http://www.ncbi.nlm.nih.gov/pubmed/29948344

SOUTH ASIA FORUM

Biochemical and molecular characterization of adult patients with type I Gaucher disease and carrier frequency analysis of Leu444Pro – a common Gaucher disease mutation in India

Jayesh Sheth, Dhairya Pancholi, Mehul Mistri, Payal Nath, Chitra Ankleshwaria, Riddhi Bhavsar , Ratna Puri, Shubha Phadke, Frenny Sheth

BMC Medical Genetics (2018) 19:178

BACKGROUND: Gaucher disease is a rare pan-ethnic disorder which occurs due to an increased accumulation of

Society for Indian Academy of Medical Genetics

SANOFI GENZYME

SIAMG-GENZYME FELLOWSHIP IN CLINICAL GENETICS

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 - Thiruvananthapuram.

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.

Applications invited for 3-month fellowship program.

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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lsdinfoindia@sanofi.com

undegraded glycolipid glucocerebroside inside the cells' lysosomes. A beta-Glucosidase (GBA) gene defect results in glucocerebrosidase enzyme deficiency. Though the disease is mainly diagnosed in childhood, the adult manifestation is often missed or identified late due to the failure to recognize the heterogeneous clinical presentation. The present study includes seven unrelated Indian adult patients (age range: 20–40 years) having splenomegaly, with or without hepatomegaly, cytopenia and bone abnormality.

METHODS: The biochemical investigation implicated measuring plasma chitotriosidase enzyme activity followed by confirmatory test of β-Glucosidase enzyme activity from the leukocytes. The molecular characterization involved patients' initial screening for the common Gaucher mutation (Leu444Pro). Later, all patients were subjected to whole GBA gene coding region study using bidirectional Sanger sequencing. The population screening for common Gaucher disease mutation (Leu444Pro) was executed in 1200 unrelated and healthy Indian subjects by Restriction Fragment Length Polymorphism-Polymerase Chain Reaction technique. The allele frequency was calculated using HardyWeinberg formula.

RESULTS: The biochemical analysis revealed a significant reduction in the β-Glucosidase activity in all the patients. Also, an elevated level of plasma Chitotriosidase activity in five patients supported their diagnosis of Gaucher disease. Sanger sequencing established four patients with homozygous variation and three patients with compound heterozygous variation in GBA gene. This study uncovers two missense variants (Ala448Thr and Val17Gly) not previously reported in Gaucher disease patients. Also the known mutations like Leu444Pro, Arg329Cys, Asp315Asn, Ser125Arg, and Arg395Cys were identified in these patients. The homology modeling suggested the destabilization of the protein structure due to novel variants. The Leu444Pro mutation screening in the Indian population spotted two people as a carrier. This emerged the carrier frequency of 1:600 along with wild-type allele frequency 0.97113 and mutant allele frequency 0.02887

CONCLUSIONS: The study reports novel and known variants identified in the GBA gene in seven adult patients. The given study is the first report on the carrier frequency of the Leu444Pro mutant allele in an Indian population which will help understanding the burden and susceptibility of Gaucher disease to affect next generation in India

https://bmcmedgenet.biomedcentral.com/track/pdf/10.1186/s12881-018-0687-5

Knowledge Forum

1. Pulmonary involvement occurs in all three types of Niemann-Pick disease, but most frequently in type B.
   https://www.ncbi.nlm.nih.gov/pubmed/27164983
2. Non-inflammatory joint stiffness or pain, carpal tunnel syndrome, trigger fingers, unexplained pain crises and short stature should all prompt consideration of a lysosomal storage disorder.
   https://www.ncbi.nlm.nih.gov/pubmed/27124840
3. Along with visceral, hematologic, and bone manifestations in Gaucher disease, patients may experience chronic fatigue resulting in functional disability and reduced quality of life.
   https://www.ncbi.nlm.nih.gov/pubmed/27129405

Sanofi, D-2, 2nd Floor, Southern Park,
Saket District Center, Saket, New Delhi - 110017
☎ 011 40558000

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

ABRIDGED PRESCRIBING INFORMATION

Cerezyme® (imiglucerase)

Imiglucerase for Injection 400 Units
Lyophilized 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-Synthelabo (I) Pvt Ltd, Sanofi House, CT Survey No 117-B, L&T Business Park, Saki Vihar Road, Powai, Mumbai - 400072

Source: Cerezyme India Prescribing Information dated April 2017
Date: August 2017

Myozyme® (alglucosidase alfa)

Alglucosidase alfa for injection (r-DNA origin) 50mg
Lyophilized Powder 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-Synthelabo (I) Pvt Ltd, Sanofi House, CT Survey No 117-B, L&T Business Park, Saki Vihar Road, Powai, Mumbai - 400072

Source: Myozyme India Prescribing Information dated September 2014
Date: August 2017

ALDURAZYME® (LARONIDASE)

Laronidase Solution for Injection
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-Synthelabo (I) Pvt Ltd, Sanofi House, CT Survey No 117-B, L&T Business Park, Saki Vihar Road, Powai, Mumbai - 400072

Source: Aldurazyme India Prescribing Information dated June 2016
Date: August 2017

Fabrazyme® agalsidase beta

Agalsidase beta for infusion
Powder for concentrate for solution

COMPOSITION: Each 35 mg vial of Fabrazyme® 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. 35 mg (7 mL) may be extracted from the vial.

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

DOSAGE & ADMINISTRATION: The recommended dose of Fabrazyme® is 1.0 mg/kg body weight infused every 2 weeks as an IV infusion. In clinical trials, the initial IV infusion rate was administered at a rate of no more than 0.25 mg/min or 15 mg/hr. The infusion rate may be slowed in the event of infusion-associated reactions. After patient tolerance has been established, the infusion rate may be increased gradually with subsequent infusions, as tolerated. Overall, the safety and efficacy of Fabrazyme®-treatment administered at 1.0 mg/kg every 2 weeks in children between the ages of 8 and 16 years is consistent with that seen in adults. The safety and efficacy of Fabrazyme® at this dose in patients younger than 8 years of age have not been evaluated. The safety and efficacy of Fabrazyme® in patients older than 65 years have not been established. No changes in dose are necessary for patients with renal insufficiency. Studies in patients with hepatic insufficiency have not been performed.

SAFETY RELATED INFORMATION:

Contraindications: No specified.

Warnings & Precautions: As with any intravenously administered protein product, patients may develop antibodies to the protein and immune-mediated reactions are possible. Most patients develop IgG antibodies to Fabrazyme®. Patients with antibodies to r-hαGAL have a higher risk of infusion-associated reactions.

Patients treated with Fabrazyme® may develop infusion-associated reactions the majority of which are mild to moderate in intensity. If an infusion-associated reaction occurs during a Fabrazyme® infusion, decreasing the infusion rate, temporarily stopping the infusion and/or administration of antipyretics, antihistamines, and/or steroids may ameliorate the symptoms. If severe allergic or anaphylactoid reactions occur, immediate discontinuation of the administration of Fabrazyme® and current medical standards for emergency treatment are to be provided. The risks and benefits of re-administering Fabrazyme® following a severe hypersensitivity or anaphylactoid reaction should be considered.

Patients who have had a positive skin test or who have tested positive for IgE antibodies to r-hαGAL have been successfully rechallenged with Fabrazyme®. The initial rechallenge administration should be at a low dose and a lower infusion rate (1/2 the therapeutic dose (0.5mg/kg) at 1/25 the initial standard recommended rate (0.01mg/min)). 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.

It is suggested that patients be monitored periodically for IgG antibody formation.

Pregnancy: Reproduction studies have been performed in rats at doses up to 10mg/kg/day in the fertility study and 30 mg/kg/day in the embryo-fetal development study. These studies have revealed no evidence of impaired fertility or harm to the fetus due to Fabrazyme®. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

No studies of perinatal toxicity have been performed.

Labor and Delivery: not specified.

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: *Frequently reported adverse reactions:* Infusion-associated reactions (IARs): These IARs included events of chills, fever (pyrexia/body temperature increased/hyperthermia), temperature change sensation (feeling cold/feeling hot), nausea, vomiting, hypertension (blood pressure increased), flushing (hot flush), paraesthesia (burning sensation), fatigue (lethargy/malaise/asthenia), pain (pain in extremity), headache, pruritus (pruritus generalized), chest pain (chest discomfort), urticaria, dyspnea (dyspnea exacerbated), dizziness, pallor, somnolence, and tachycardia.

For full prescribing information please contact: Sanofi-Synthelabo (I) Pvt Ltd, Sanofi House, CT Survey No 117-B, L&T Business Park, Saki Vihar Road, Powai, Mumbai - 400072.

Source: Fabrazyme India Prescribing Information dated February 2017
Date: August 2017