Medical Policy

BlueCross BlueShield of Kansas
An independent licensee of the Blue Cross Blue Shield Association

Title: Lysosomal Storage Disorders

- **Prime will review Prior Authorization requests.**

Prior Authorization Form:

http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-Fabry-Disease.pdf
http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-Gaucher-Disease.pdf
http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-Hunter-Syndrome.pdf
http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-Hurler-and-Hurler-Scheie-Syndrome.pdf
http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-Lysosomal-Acid-Lipase-Deficiency.pdf
http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-Maroteaux-Lamy-Syndrome.pdf
http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-Morquio-A-Syndrome.pdf
https://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-MPS-VII-Sly-Syndrome.pdf
http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-Pompe-Disease.pdf

Link to Drug List (Formulary):

http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.shtml

Professional
Original Effective Date: August 1, 2015
Revision Date(s): August 1, 2015; February 1, 2016; August 1, 2016; January 1, 2017, July 15, 2017; June 15, 2018
Current Effective Date: June 15, 2018

Institutional
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Current Effective Date: June 15, 2018

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

DESCRIPTION

The intent of the lysosomal storage disorder medical drug criteria is to ensure appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines and according to dosing recommended in product labeling. The criteria will consider these agents appropriate for patients with a FDA labeled indication. Dosing will be limited to the FDA labeled dosage for the specific indication.

Target Agents

▪ **Aldurazyme®** (laronidase) ▪ **Cerezyme®** (imiglucerase) ▪ **Elaprase®** (idursulfase) ▪ **Elelyso®** (taliglucerase) ▪ **Fabrazyme®** (agalsidase) ▪ **Kanuma**™ (sebelipase alfa)	▪ **Lumizyme®** (alglucosidase) ▪ **Mepsevii**™ (vestronidase alfa-vjbk) ▪ **Naglazyme®** (galsulfase) ▪ **Vimizim™** (elosulfase) ▪ **Vpriv®** (velaglucerase)

FDA Approved Indications and Dosage[3-11,32,42,50]

Agents	FDA Labeled Indications	Dosing
Aldurazyme (laronidase)	Hurler and Hurler-Scheie MPS 1 and the Scheie form who have moderate to severe symptoms	0.58 mg/kg once weekly
Cerezyme (imiglucerase)	Adults and pediatrics: Type 1 Gaucher disease that results in one or more of the following conditions: anemia, thrombocytopenia, bone disease, hepatomegaly or splenomegaly -	2.5 U/kg 3 times per week – 60 U/kg once every 2 weeks.
Elaprase (idursulfase)	Hunter Syndrome MPS II	0.5 mg/kg once weekly
Eylelyso (taliglucerase)	Adults and pediatrics ≥ 4 years old: Type 1 Gaucher disease	60 units/kg every other week
Fabrazyme (agalsidase)	Fabry disease	1 mg/kg every 2 weeks
Kanuma (sebelipase alfa)	Lysosomal Acid Lipase (LAL) deficiency	Rapidly Progressive LAL Deficiency Presenting in the first 6 months of life: 1 mg/kg IV once weekly. Those that do not achieve optimal clinical response, increase to 3 mg/kg once weekly Pediatric and Adult Patients: 1 mg/kg IV once every other week
Lumizyme (alglucosidase)	Pompe disease (acid α-glucosidase (GAA) deficiency)	20 mg/kg every 2 weeks
Mepsevii™ (vestronidase alfa-vjbk)	Mucopolysaccharidosis VII (MPS VII, Sly syndrome) Limitations of Use	4 mg/kg every 2 weeks

Agents	FDA Labeled Indications	Dosing
	The effect of Mepsevii on the central nervous system manifestations of MPS VII has not been determined	
Naglazyme (galsulfase)	Maroteaux-Lamy syndrome MPS VI	1 mg/kg once weekly
Vimizim (elosulfase)	Morquio A Syndrome (MPS IVA)	2 mg/kg once weekly
Vpriv (velaglucerase)	Adults and pediatrics ≥ 4 years old: Type 1Gaucher disease	60 units/kg every other week

MPS=mucopolysaccharidosis

POLICY

Gaucher Disease

Initial Evaluation

Cerezyme, Elelyso, and Vpriv will be approved when ALL of the following are met:

1. ONE of the following:
   A. BOTH of the following:
      i. There is documentation that the patient is already being treated with the requested agent:
      AND
      ii. The prescriber has documented current levels of the following: hemoglobin levels, platelet count, liver and spleen volumes, status of bone pain, and if applicable patient's growth velocity

   OR

   B. The patient has a diagnosis of Gaucher disease Type 1 and ALL of the following:
      i. The patient does NOT have any neuropathic symptoms [e.g. convulsive crisis, ataxia, supranuclear horizontal ocular palsy, dementia, alteration in ocular movement, bulbar (swallowing difficulties, stridor, convergent strabismus)]
      AND
      ii. If the requested agent is Eleyso or Vpriv, the patient is 4 years old or older
      AND
      iii. ONE of the following
         1) The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist)
         OR
         2) The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis

      AND

iv. ONE of the following:
1) The patient has glucocerebrosidase activity of <15% of mean normal in fibroblasts leukocytes, or other nucleated cells
OR
2) The patient has genetic analysis with disease causing mutations on 2 alleles of glucocerebrosidase genome
AND

v. The patient has ONE of the following:
1) Anemia defined as mean hemoglobin (Hb) level below the testing laboratory's lower limit of normal range based on age and gender
OR
2) Platelet count of < 100,000/µL on at least 2 measurements
OR
3) Hepatomegaly
OR
4) Splenomegaly
OR
5) Growth failure (growth velocity below the standard mean for age)
OR
6) Evidence of bone disease with other causes ruled out
AND

vi. If the client has a preferred agent, then ONE of the following:
1) The patient has tried the preferred agent
OR
2) The patient has a documented intolerance, FDA labeled contraindication or hypersensitivity to the preferred agent

AND

2. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent
AND
3. The dose is within the FDA labeled dose

Length of Approval: 12 months

Renewal Evaluation

1. The patient has been previously approved for therapy through Prime Therapeutics Medical Drug Review process for the requested agent
AND
2. ONE of the following:
A. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist)
OR

B. The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis

AND

3. The patient has shown improvement in or stabilization of at least **ONE** of the following:
   A. Hemoglobin levels
      OR
   B. Platelet count sufficiently to decrease the risk of bleeding
      OR
   C. Liver or spleen volumes
      OR
   D. Growth
      OR
   E. Bone pain or disease

   AND
4. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent

   AND
5. The dose is within the FDA labeled dose

Length of Approval: 12 months

Pompe Disease

Initial Evaluation

Lumizyme will be approved when ALL of the following are met:

1. ONE of the following:
   A. There is documentation that the patient is already being treated with the requested agent
      OR
   B. The patient has a diagnosis of Pompe disease (acid alpha-glucosidase deficiency) and BOTH of the following:
      i. ONE of the following:
         1) The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist)
            OR
         2) The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis

         AND
      ii. The patient was diagnosed by ONE of the following:
         1) Prenatal diagnosis via chorionic villus biopsies and/or cultured amniotic cells
            OR

2) Genetic testing confirming two pathogenic mutations on separate alleles in the GAA gene
OR
3) Diagnosis by TWO of the following:
   a. Dried blot spot enzyme assay
   b. Skin fibroblast enzyme assay
   c. Lymphocytes
   d. Mixed leukocytes
   e. Urinary tetrasaccharides
   f. Skeletal muscle biopsy

AND

2. The patient is not receiving invasive ventilation due to respiratory failure
AND
3. The prescriber has evaluated current status of one or more of the following:
   A. Gross motor function (e.g. PEDI-Pompe scale)
   OR
   B. Swallowing (e.g. videofluoroscopy)
   OR
   C. Neurological function
   OR
   D. Pulmonary function (e.g. FVC % predicted)
   OR
   E. Liver or spleen volumes
   OR
   F. Growth (if applicable)
   OR
   G. Cardiac function (e.g. cardiomyopathy)
   AND
4. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent
AND
5. The dose is within the FDA labeled dose

Length of Approval: 12 months

Renewal Evaluation

1. The patient has been previously approved for therapy through Prime Therapeutics Medical Drug Review process for the requested agent
AND
2. ONE of the following:
   A. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist)
   OR

B. The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis

AND

3. The patient has shown improvement in or stabilization of at least ONE of the following:
   A. Gross motor function (e.g. PEDI-Pompe scale)
      OR
   B. Swallowing (e.g. videofluoroscopy)
      OR
   C. Neurological function
      OR
   D. Pulmonary function (e.g. FVC % predicted)
      OR
   E. Liver or spleen volumes
      OR
   F. Growth
      OR
   G. Cardiac function

   AND
4. The patient is not receiving invasive ventilation due to respiratory failure

   AND
5. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent

   AND
6. The dose is within the FDA labeled dose

Length of Approval: 12 months

Hunter Syndrome [Mucopolysaccharidosis type II (MPS II)]

Initial Evaluation

Elaprase will be approved when ALL of the following are met:

1. ONE of the following:
   A. BOTH of the following:
      i. There is documentation that the patient is already being treated with the requested agent:
      AND
      ii. The prescriber has documented current levels for joint mobility, walking capacity, ejection fraction, forced vital capacity, liver and spleen volume, (and if applicable sleep apnea/desaturation sleep study results)
   OR
   B. The patient has a diagnosis of Hunter Syndrome [mucopolysaccharidosis type II (MPS II)] and ALL of the following:
      i. ONE of the following:
         1) The patient has an iduronate-2-sulfatase deficiency in leukocytes, fibroblasts, or plasma and has a normal enzyme activity in at least one other sulfatase enzyme
         OR
         2) The patient has genetic analysis of disease causing mutation of the iduronate 2-sulfatase gene
      AND
      ii. ONE of the following:
         1) The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist)
         OR
         2) The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis
      AND
      iii. ONE of the following:
         1) In an overnight sleep study, the patient has had either an average of > 5 apnea events per hour (>1 apnea event per hour for children) over the patient's total sleep OR more than 2 severe episodes of desaturation (mean nocturnal O2 saturation of <85% in adults; <92% in children)
         OR
         2) The patient has a forced vital capacity (FVC) < 80% predicted value for height
         OR
         3) The patient has a reduced ejection fraction of <56% [normal range 56-78%]
         OR

4) The patient has a reduction in fraction shortening to <25% [normal range 25-46%]
OR
5) The patient has a restricted range of movement in joints of > 10° from normal
OR
6) The patient has hepatomegaly
OR
7) The patient has splenomegaly

AND

2. The patient does not have any FDA labeled dose contraindication(s) to therapy with the requested agent
AND
3. The dose is within the FDA labeled dose

Length of Approval: 12 months

Renewal Evaluation

1. The patient has been previously approved for therapy through Prime Therapeutics Medical Drug Review process for the requested agent
AND
2. ONE of the following:
   A. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist)
   OR
   B. The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis

AND

3. The patient has shown improvement in or stabilization of at least ONE of the following:
   A. Joint mobility
   OR
   B. Walking capacity
   OR
   C. Ejection fraction
   OR
   D. Fraction shortening
   OR
   E. Forced vital capacity
   OR
   F. Liver or spleen volume
   OR

G. Sleep apnea/severity of desaturation episodes

AND

4. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent

AND

5. The dose is within the FDA labeled dose

Length of Approval: 12 months

Fabry Disease

Initial Evaluation

Fabrazyme will be approved when ALL of the following are met:

1. ONE of the following:
   A. There is documentation that the patient is already being treated with the requested agent

   OR

   B. The patient has a diagnosis of Fabry disease and BOTH of the following:
      i. ONE of the following:
         1) The patient is male and has a deficiency in α-galactosidase A (alpha GAL A) activity in leukocytes, fibroblasts, or plasma

         OR

         2) The patient is female and has a diagnosis based on mutation of the alpha-GAL A

      AND

      ii. ONE of the following:
         1) The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist)

         OR

         2) The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis

   AND

2. The prescriber has documented current levels of the following: kidney function (Proteinuria, GFR) Cardiac function (Left ventricular hypertrophy, Conduction or rhythm, Mitral or aortic insufficiency), Optic neuropathy, Neuropathic pain, and Gastrointestinal symptoms

   AND

3. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent

   AND

4. The dose is within the FDA labeled dose

Length of Approval: 12 months

Renewal Evaluation

1. The patient has been previously approved for therapy through Prime Therapeutics Medical Drug Review process for the requested agent
   AND
2. ONE of the following:
   A. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist)
      OR
   B. The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis
   AND
3. The patient has shown improvement in or stabilization of at least ONE of the following:
   A. GFR
      OR
   B. Proteinuria
      OR
   C. Left ventricular hypertrophy
      OR
   D. Conduction or rhythm
      OR
   E. Mitral or aortic insufficiency
      OR
   F. Optic neuropathy
      OR
   G. Neuropathic pain
      OR
   H. Gastrointestinal symptoms
   AND
4. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent
   AND
5. The dose is within the FDA labeled dose

Length of Approval: 12 months

Maroteaux-Lamy Syndrome [Mucopolysaccharidosis type (VI MPS VI)]

Initial Evaluation

Naglazyme will be approved when ALL of the following are met:

1. ONE of the following:
   A. BOTH of the following:
      i. There is documentation that the patient is already being treated with the requested agent
      AND
      ii. The prescriber has documented current levels for joint mobility, walking capacity, ejection fraction, forced vital capacity, liver and spleen volume, (and if applicable sleep apnea/desaturation sleep study results)
   OR
   B. The patient has a diagnosis of Maroteaux-Lamy Syndrome [Mucopolysaccharidosis type VI (MPS IV)] and ALL of the following:
      i. ONE of the following:
         1) The patient has an arylsulfatase B enzyme activity of <10% of the lower limit of normal in cultured fibroblasts and has normal enzyme activity in at least one other sulfatase enzyme
         OR
         2) The patient has genetic analysis with disease causing mutation in the arylsulfatase B gene
      AND
      ii. ONE of the following:
         1) The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist)
         OR
         2) The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis
      AND
      iii. ONE of the following:
         1) In an overnight sleep study the patient has had either an average of >5 apnea events per hour (>1 apnea event per hour for children) over the patient's total sleep OR more than 2 severe episodes of desaturation (mean nocturnal O2 saturation of <85% in adults; <92% in children)
         OR
         2) The patient has a forced vital capacity (FVC) < 80% predicted value for height
         OR
         3) The patient has a reduced ejection fraction of <56% [normal range 56-78%]
         OR

4) The patient has a reduction in fraction shortening to <25% [normal range 25-46%]
OR
5) The patient has a restricted range of movement in joints of > 10◦ from normal
OR
6) The patient has a splenomegaly
OR
7) The patient has a hepatomegaly

AND

2. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent
AND
3. The dose is within the FDA labeled dose

Length of Approval: 12 months

Renewal Evaluation

1. The patient has been previously approved for therapy through Prime Therapeutics Medical Drug Review process for the requested agent
AND
2. ONE of the following:
   A. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist)
   OR
   B. The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis

AND

3. The patient has shown improvement in or stabilization of at least ONE of the following:
   A. Joint mobility
   OR
   B. Walking capacity
   OR
   C. Ejection fraction
   OR
   D. Fraction shortening
   OR
   E. Forced vital capacity
   OR
   F. Liver or Spleen volume
   OR

G. Sleep apnea/severity of desaturation episodes
AND

4. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent
AND
5. The dose is within the FDA labeled dose

Length of Approval: 12 months

Hurler Hurler-Scheie, and Sheie Syndrome (Mucopolysaccharidosis type I [MPS I])

Initial Evaluation

Aldurazyme will be approved when ALL of the following are met:

1. ONE of the following:
   A. BOTH of the following:
      i. There is documentation that the patient is already being treated with the requested agent
      AND
      ii. the prescriber has documented current levels for joint mobility, walking capacity, ejection fraction, forced vital capacity, liver and spleen volumes (and if applicable sleep apnea/desaturation sleep study results)
   OR
   B. The patient has a diagnosis of Hurler, Hurler-Scheie or Scheie Syndrome [Mucopolysaccharidosis type I (MPS I)] and ALL of the following:
      i. ONE of the following:
         1) The patient has α-L-iduronidase enzyme activity of <10% of average reference values in leukocytes, fibroblasts, plasma or serum and has normal enzyme activity in at least one other sulfatase enzyme
         OR
         2) The patient has genetic analysis with disease causing mutation of the α-L-iduronidase gene
      AND
      ii. ONE of the following:
         1) The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist)
         OR
         2) The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis
      AND

iii. ONE of the following:
1) In an overnight sleep study the patient has had either an average of >5 apnea events per hour (>1 apnea event per hour for children) over the patient's total sleep OR more than 2 severe episodes of desaturation (mean nocturnal O2 saturation of <85% in adults; <92% in children)
OR
2) The patient has a forced vital capacity (FVC) < 80% predicted value for height
OR
3) The patient has a reduced ejection fraction of <56% [normal range 56-78%]
OR
4) The patient has a reduction in fraction shortening to <25% [normal range 25-46%]
OR
5) The patient has a restricted range of movement in joints of > 10◦ from normal
OR
6) The patient has hepatomegaly
OR
7) The patient has a splenomegaly

AND

2. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent
AND
3. The dose is within the FDA labeled dose

Length of Approval: 12 months

Renewal Evaluation

1. The patient has been previously approved for therapy through Prime Therapeutics Medical Drug Review process for the requested agent
AND
2. ONE of the following:
A. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist)
OR
B. The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis

AND

3. The patient has shown improvement in or stabilization of at least ONE of the following:
   A. Joint mobility
      OR
   B. Walking capacity
      OR
   C. Ejection fraction
      OR
   D. Fraction shortening
      OR
   E. Forced vital capacity
      OR
   F. Liver or spleen volume
      OR
   G. Sleep apnea/severity of desaturation episodes
   AND
4. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent
   AND
5. The dose is within the FDA labeled dose

Length of Approval: 12 months

Morque A Syndrome [Mucopolysaccharidosis type IVA (MPS IVA)]

Initial Evaluation

Vimizim will be approved when ALL of the following are met:

1. ONE of the following:
   A. There is documentation that the patient is already being treated with the requested agent
      OR
   B. The patient has a diagnosis of Morquio A Syndrome [Mucopolysaccharidosis type IVA (MPS IVA)] and BOTH of the following:
      i. The patient has a N-acetylgalactosamine 6-sulfatase (GALNS) deficiency as diagnosed by ONE of the following:
         1. Prenatal diagnosis via chorionic villus biopsies and/or cultured amniotic cells
            OR
         2. The patient has a N-acetylgalactosamine 6-sulfatase (GALNS) deficiency in leukocytes or fibroblasts
            OR

3. Genetic analysis with disease causing mutation of the N-acetylgalactosamine 6-sulfatase (GALNS) gene
   AND

ii. ONE of the following:
   1. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist)
      OR
   2. The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis

AND

2. The prescriber has documented the current walking capacity
   AND
3. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent
   AND
4. The dose is within the FDA labeled dose

Length of approval: 12 months

Renewal Evaluation

1. The patient has been previously approved for therapy through Prime Therapeutics Medical Drug Review process for the requested agent
   AND
2. ONE of the following:
   A. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist)
      OR
   B. The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis

   AND
3. The patient has shown improvement in or stabilization in walking capacity
   AND
4. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent
   AND
5. The dose is within the FDA labeled dose

Length of approval: 12 months

Lysosomal Acid Lipase Deficiency (LAL-D)

Initial Evaluation

Kanuma will be approved when ALL of the following are met:

1. ONE of the following:
   A. There is documentation that the patient is already being treated with the requested agent
   OR
   B. ALL of the following:
      i. The patient has a Lysosomal Acid Lipase Deficiency (LAL-D) as diagnosed by ONE of the following:
         1) Dried Blood Spot (DBS) testing
         OR
         2) Genetic analysis with the disease causing mutations on the *LIPA* gene
         OR
         3) Measurement of lysosomal acid lipase activity in peripheral blood mononuclear cells or cultured fibroblasts
      AND
      ii. ALL of the following:
         1) The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist)
         OR
         2) The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis
      AND
      iii. If the patient has the cholesteryl ester storage disease variant (CESD), then ONE of the following:
         1) The patient has failed maximally tolerated statin therapy
         OR
         2) The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to all statins

   AND
2. The prescriber has documented current levels of growth (if applicable), lipid levels (LDL-c, TG, non-HDL-c, HDL-c), and liver volume
   AND
3. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent
   AND
4. The dose is within the FDA labeled dose

Length of approval: 12 months

Renewal Evaluation

1. The patient has been previously approved for therapy through Prime Therapeutics Medical Drug Review process for the requested agent
   AND
2. ONE of the following:
   A. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist)
      OR
   B. The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis
   AND
3. The patient has shown improvement in or stabilization of at least ONE of the following:
   A. Growth
      OR
   B. Lipid levels (LDL-c, TG, non-HDL-c, HDL-c)
      OR
   C. Liver volume
   AND
4. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent
   AND
5. The dose is within the FDA labeled dose

Length of approval: 12 months

Mucopolysaccharidosis VII (MPSVII) (Sly syndrome)

Initial Evaluation

Mepsevii will be approved when ALL of the following are met:

1. ONE of the following:
   A. BOTH of the following:
      i. There is documentation that the patient is already being treated with the requested agent
      AND
      ii. The prescriber has documented current levels for joint mobility, walking capacity, ejection fraction, forced vital capacity, liver and spleen volume, (and if applicable sleep apnea/desaturation sleep study results)

   OR

   B. The patient has a diagnosis of Sly Syndrome [mucopolysaccharidosis type VII (MPS VII)] and ALL of the following:
      i. ONE of the following:
         1) The patient has a beta-glucuronidase deficiency in leukocytes, fibroblasts, or plasma
         OR
         2) The patient has genetic analysis of disease causing mutation of the beta-glucuronidase gene

      AND

      ii. ONE of the following:
         1) The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist)
         OR
         2) The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis

      AND

      iii. ONE of the following:
         1) In an overnight sleep study the patient has had either an average of >5 apnea events per hour (>1 apnea event per hour for children) over the patient's total sleep OR more than 2 severe episodes of desaturation (mean nocturnal O2 saturation of <85% in adults; <92% in children)
         OR
         2) The patient has a forced vital capacity (FVC) < 80% predicted value for height
         OR
         3) The patient has reduced ejection fraction of <56% [normal range 56-78%]
         OR

4) The patient has a reduction in fraction shortening to <25% [normal range 25-46%]
OR
5) The patient has restricted range of movement in joints of > 10° from normal
OR
6) The patient has hepatomegaly
OR
7) The patient has splenomegaly

AND

2. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent
AND
3. The dose is within the FDA labeled dose

Length of Approval: 12 months

Renewal Evaluation

1. The patient has been previously approved for therapy through Prime Therapeutics Medical Drug Review process for the requested agent
AND
2. ONE of the following:
   A. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist)
   OR
   B. The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis
AND
3. The patient has shown improvement in or stabilization of at least ONE of the following:
   A. Joint mobility
   OR
   B. Walking capacity
   OR
   C. Ejection fraction
   OR
   D. Fraction shortening
   OR
   E. Forced vital capacity
   OR
   F. Liver or spleen volume
   OR
   G. Sleep apnea/severity of desaturation episodes

AND

4. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent

AND

5. The dose is within the FDA labeled dose

Length of Approval: 12 months

Agent	Contraindications
Aldurazyme (laronidase)	None
Cerezyme (imiglucerase)	None. Treatment should be carefully re-evaluated if there is significant clinical evidence of hypersensitivity to the product
Elaprase (idursulfase)	None
Elelyso (taliglucerase)	None
Fabrazyme (agalsidase)	None
Kanuma (sebelipase alfa)	None
Lumizyme (alglucosidase)	None
Mepsevii (vestronidase alfa-vjbk)	None
Naglazyme (galsulfase)	None
Vimizim (elosulfase)	None
Vpriv (velaglucerase)	None

RATIONALE[1,49]

Lysosomal storage disorders (LSDs) are a group of inherited metabolic disorders that result in the accumulation of undigested macromolecules due to the dysfunction of lysosomes. There are several different LSDs but they share a common feature of an error of metabolism of lipids, glycoproteins, or glycosaminoglycans (GAGs), typically due to a deficiency in of a lysosomal enzyme or transport protein. A deficit in these enzymes results in progressive accumulation of material in organs and tissues which results in an increase in the size and quantity of organelles and ultimately in cellular dysfunction and organ failure. The majority of these disorders have substantial neurological involvement with developmental regression, seizures and learning difficulties. Most patients affected by these disorders have a decreased life expectancy with considerable morbidity.[1]

Most of these disorders have a birth prevalence of < 1:100,000 with a combined prevalence of around 1 in every 7,000 to 8,000 births. There isn't a cure or definitive treatment available for any LSD. Enzyme replacement therapy (ERT) is available for some LSDs and is generally considered safe.

Fabry Disease[10,18,19-21]

Fabry disease is an inherited (X-linked) lysosomal storage disorder due to a deficiency in α-galactosidase A that affects multiple organ systems. The rate of disease progression and organ damage vary with renal failure, cardiovascular disease and stroke being the major causes of morbidity and mortality typically in the fourth to fifth decade of life. It is estimated that Fabry disease affects 1 in 40,000-60,000 males in the United States. There are 2 categories of classic disease (early and late manifestations) and atypical disease. Early manifestations begin in

childhood or adolescence with the hallmark presentation of pain in the extremities (acroparesthesia), hypohidrosis, skin lesions, chronic abdominal pain and diarrhea. Late stage of the disease involves progressive deterioration of renal, cardiac, and nervous system dysfunction. Atypical disease results from individuals who have some residual enzyme activity. These patients may not show symptoms in childhood and have limited organ systems affected.

Disease management is individualized and intended to alleviate symptoms (e.g. pain management with gabapentin, carbamazepine; management of gastrointestinal symptoms with pancrelipase, metoclopramide, loperamide, and ranitidine) and to delay or prevent serious organ damage. Enzyme replacement therapy with agalsidase is intended to reverse the metabolic abnormalities in tissues and cells which should result in symptom improvement and prevention of disease complications. Agalsidase beta is FDA indicated to reduce globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types (surrogate endpoint). However, the relationship of GL-3 inclusion reduction to specific clinical manifestations of Fabry disease has not been established.

Fabry Disease is a progressive disease and can cause irreversible damage. Reviews and guidelines evaluate and confirm established efficacy for the use of enzyme replacement therapy in treating Fabry disease. They also recommend early detection and enzyme replacement therapy with agalsidase to delay progression, prevent renal, cardiac, or cerebrovascular events and improve survival. Diagnosis of enzyme activity of the α-galactosidase A activity in leukocytes or dried blood spots typically confirms diagnosis in male patients with genetic analysis looking for mutations in the GLA gene required for females as they often have enzyme levels within the normal range.

Gaucher's Disease[2,7-8,29-30,48]

Gaucher's disease is an inherited lipid storage disorder resulting from the deficiency of glucocerebrosidase. Severity varies significantly with some patients presenting in childhood with multiple complications and others remaining asymptomatic until late adulthood. There are 3 subtypes based on the absence or presence of neurologic involvement and disease progression. Type 1 is a nonneuropathic form often presenting in childhood (presents with hepatosplenomegaly [hepatomegaly is defined as a liver mass > 1.25 times the normal 2.5% of total body weight; splenomegaly is defined as a splenic mass > the normal 0.2% of total body weight in kg], pancytopenia, and skeletal disease), Type 2 is an acute, rapidly progressive neuropathic form causing death during infancy or the first years of life and Type 3 is a chronic, less progressive neuropathic form. Factors thought to contribute to the neurologic involvement of Type 2 and 3 include accumulation of glucosylsphingosine (a cytotoxic agent) in the brain. Gaucher cells are macrophages engorged with lipid with a crumple-tissue-paper appearance with displaced nuclei. Accumulation of glycolipid in the bone marrow, liver, spleen, lungs and other organs results in pancytopenia, hepatosplenomegaly, and diffuse infiltrative pulmonary disease. Diagnosis can be confirmed via measurement of glucocerebrosidase activity in leukocytes fibroblasts, or other nucleated cells. A finding of <15% of mean normal is diagnostic of disease. These patients often have anemia, thrombocytopenia, and leucopenia but diagnosis is differentiated from chronic myeloid leukemia and lymphomas with expression in peripheral blood bone marrow biopsy and aspirate showing infiltration of Gaucher cells. Anemia is defined as a mean hemoglobin (Hb) concentrations: Hb <12.0 g/dL in males >12 years of age and <11.0 g/dL for females >12 years of age; Hb < 10.5 g/dL for children > 2 but < 12 years; Hb < 9.5 g/dL for children >6 months and < 2 years and < 10.1 g/dL for children < 6 months, however,

other standards have been quoted by varying organizations.[8] Thrombocytopenia sufficient to justify ERT therapy is defined as a repeated platelet count < 100,000/µL.

Enzyme replacement therapy (ERT) [imiglucerase, velaglucerase, or taliglucerase] is the standard of care for type 1 patients who exhibit clinical signs and symptoms including anemia, thrombocytopenia, skeletal disease, or visceromegaly. Both velaglucerase and taliglucerase have demonstrated equivalent maintenance of hemoglobin and platelet counts to imiglucerase in patients previously treated with imiglucerase. ERT has been shown to decrease hepatomegaly by an average of 25% with average increases in hemoglobin on 1.5 g/dL. Skeletal disease and platelet counts are slower to respond to therapy and can take a year or more. Response to therapy varies by patient but isn't correlated to genotype, severity, splenectomy or age. ERT dosing is typically given every other week at high doses but can be given every week at a medium dose or multiple times a week at low doses. Positive results have been seen with all dosing regimens and controversy exists on the most suitable initial and maintenance dosing regimens.

Hunter Syndrome[15-17,40]

Hunter syndrome also known as mucopolysaccharidosis type II (MPS II) is an inherited lysosomal enzyme disorder resulting from a deficiency of iduronate sulfatase. This is an X-linked disorder so it affects males more than females. The disease is a chronic progressive course with involvements of multiple systems including facial coarsening, hepatomegaly, excretion of urinary glycosaminoglycans (GAGs), and leukocyte inclusion bodies.

There are 2 forms of Hunter syndrome. A severe form (type A) and a milder form (type B). These two types are distinguished by the clinical presentation as the enzyme activity is equally reduced in the assay for both types. In type A, patients present earlier in life with slow and systematic somatic and neurologic progression that ultimately leads to death by adolescence. Type B patients typically have normal intelligence but may have airway obstruction and typically develop cardiac valvular disease. They survive into adulthood and older.

Confirmation of disease and the gold standard is demonstration of a deficiency of iduronate sulfatase enzyme activity in leukocytes, fibroblasts, or plasma. Dry blood spot screening is also a valuable diagnostic method. However, this method also requires documentation of normal enzyme activity of at least one other sulfatase as low levels of iduronate sulfatase can be characteristic of other sulfatase deficiencies.

Development of any signs and symptoms of MPS II are irreversible therefore an important outcome is halting or slowing disease progression. Recommendations of treatment for MPS II is typically with idursulfase (enzyme replacement therapy) but stem cell transplantation is also an option but has shown limited clinical benefit and carries a high risk of morbidity and mortality. European recommendations for the treatment of MPS II determined it may be reasonable to offer ERT to all patients for 12 to 18 months regardless of neurocognitive status or age. These same guidelines recognize that therapy is not recommended in patients with life threatening comorbid disease for which the prognosis is unlikely to be influenced by ERT and in patients who experience life threatening reactions that are unable to be prevented with pretreatment. Therapy may improve or maintain respiratory function, organomegaly, and joint mobility. Guidelines from Australia require confirmation of diagnosis in patients without neuropathic involvement via deficiency of iduronate 2-sulfatase in white blood cells. These guidelines (along with others that

mirror similar information) identify patients who are early on in their disease to likely benefit from therapy and require patients to present with at least one of the following: apnea incidence of > 5 events/hour (>1 event/hour for children) of total sleep time or more than 2 severe episodes of desaturation in (mean nocturnal O2 saturation of <85% in adults; <92% in children) overnight sleep study; forced vital capacity (FVC) < 80% predicted value for height; reduced ejection fraction of <56% [normal range 56-78%] or a reduction in fraction shortening to <25% [normal range 25-46%]; restricted range of movement in joints of > 10° from normal in shoulders, neck, hips, knees, elbows, or hands; < 5 years of age. Patients must not be experiencing neuropathic symptoms in order to qualify for treatment. Continuation of therapy requires clinical improvement or stabilization of patient's condition.

Hurler, Hurler-Scheie, and Scheie Syndrome[26-28,40,46-47]

Hurler, Hurler-Scheie, and Scheie Syndrome are also known as Mucopolysaccharidosis I. MPS I is a rare, autosomal recessive disease with pathologic manifestations in multiple organ systems and tissues. The estimated incidence in the United States is about 1 in 100,000 births. Depending on the severity, patients may die in early childhood or live into adulthood. The disease is caused by a defect in the gene coding for the lysosomal enzyme alpha-L-iduronidase; as a result, the cells of affected individuals either are unable to produce the enzyme or produce it in low amounts. This results in an inability of the lysosome to affect the stepwise degradation of certain glycosaminoglycans (GAGs) - namely dermatan sulfate and heparan sulfate - a process essential for normal growth and homeostasis of tissues. These GAGs, which are important constituents of the extracellular matrix, joint fluid, and connective tissue throughout the body, progressively accumulate in the lysosome, ultimately causing cell, tissue, and organ dysfunction by largely unknown mechanisms.

MPS I is considered to be the prototypical lysosomal storage disorder with progressive multi-systemic disease and presenting features that vary depending on where a patient is on the disease continuum. The disease continuum is as follows (most severe to less severe): Hurler: Severe developmental delay, more progressive, severe respiratory disease, obstructive airway disease, and death (~10 years); Hurler Scheie: Little or no intellectual delay, respiratory disease, obstructive airway disease, cardiovascular disease, joint stiffness, skeletal abnormalities, decreased visual acuity, and death in teens-20's; Scheie: Normal intelligence, less physical progressive problems, corneal clouding, joint stiffness, valvular hear disease, and death in later decades.

Hemopoietic stem cell transplant (HSCT) is the treatment of choice for some patients with MPS I. Successful transplantation can preserve neurocognition, improve some aspects of somatic disease, and increase survival. Improvements and/or stabilization of myocardial function has been seen. HSCT has limited impact on bone disease. Better results have been observed in patients who undergo transplantation at <24 months of age and are able to preserve normal enzyme levels post transplant. The positive effects of HSCT are seen typically within the first few years post transplant but there is a relatively high incidence of graft failure (30%). Recent studies have estimated the overall mortality rate of HSCT to be 15%. Patients with poor clinical condition and with respiratory and cardiologic morbidities have shown to benefit from the combination of ERT and HSCT. The clinical benefits of ERT include decreased hepatomegaly, improved respiratory function, improved walking ability, increased joint range of motion, decreased left ventricular hypertrophy, improved growth, and improved quality of life. Patients eligible for therapy with laronidase should have a deficiency in α-L-iduronidase activity confirmed in 2 biological samples

(blood filter paper, leukocytes, fibroblasts, or other relevant tissues), genotyping, or both. Enzymatic activity <10% of reference average values is consistent with an MPS diagnosis. Measuring the activity of another lysosomal enzyme in the same sample is recommended for control of preservation of the material. Patient should have at least 1 clinical manifestation of MPS I known to respond to ERT therapy: obstructive, restrictive and interstitial respiratory disease, sleep apnea/hyperpnea syndrome; osteoarticular compromise with affects mobility and independence in activities of daily living; cardiac compromise (myocardiopathy, cor pulmonale). Evidence is not available for treatment or not treating patients without symptoms that are detected with neonatal or family screening.

Lysosomal Acid Lipase Deficiency (LAL-D)[42-45]

LAL-D is a progressive and rare lysosomal storage disorder characterized by a reduction or loss of lysosomal acid lipase activity (due to *LIPA* gene mutation). This subsequently causes cholesterol esters and triglycerides to accumulate in the lysosomes manifesting in several ways including dyslipidemia, accelerated atherosclerosis, and/or progressive liver disease. LAL-D severity and progression has a vast range depending on the residual enzyme activity (e.g. Wolman disease is a rapidly progressing disease of newborns whereas Cholesterol Ester Storage Disease (CESD) usually is discovered in children or young adults). Wolman's Disease, the complete loss of LAL, is estimated to have an incidence of 1 in 500,000 live births and is characterized by poor growth, vomiting, diarrhea, hepatomegaly, and historically led to death in infancy. The less severe CESD, partial loss of LAL, has an estimated prevalence of 1 in 40,000 individuals. The prevalence could possibly be under diagnosed due to the fact that many patients have no symptoms or very non-descript symptoms such as elevated liver function tests, dyslipidemia, or gastrointestinal symptoms. The manifestations of LAL-D, especially CESD, can mimic and be mistaken for other cardiovascular and liver diseases (e.g. Familial Hypercholesterolemia, Non-alcoholic Steatohepatitis, Metabolic Syndrome, etc.). Diagnosis can be made with genetic testing or measuring LAL activity levels via Dried Blood Spot testing (DBS). Some labs still perform LAL Deficiency confirmation via measurement of lysosomal acid lipase activity in peripheral blood mononuclear cells or cultured fibroblasts. Historically, treatment was limited to controlling cholesterol levels and preventing atherosclerotic events with HMG-CoA reductase inhibitors.

Maroteaux-Lamy Syndrome[17,22-25,40]

Maroteaux-Lamy syndrome, also known as Mucopolysaccharidosis type VI (MPS VI), is an inherited lysosomal storage disease that results from the deficiency of N-acetylgalactosamine 4-sulfatase and the accumulation of dermatan sulfate in lysosomes. The disease is progressive with slowly and rapidly progressive forms and involves multiple systems including skeletal, cardiac, optical, spleen, liver, lung, and dura. Neurologic symptoms are typically reserved in this disorder. The prevalence of this disorder is estimated to be 1 per 43,261 to 1 in 1,505,160 live births. Depending on the rate of progression patients may live between the 2nd and 5th decades of life. MPS VI patients typically show disease signs early in childhood with retarded growth, dysostosis multiplex, inguinal or umbilical hernias, recurrent respiratory illness, hepatosplenomegaly, and coarse facial features.

Confirmed diagnosis requires evidence of clinical phenotype with an arylsulfatase B enzyme activity <10% of the lower limit of normal in cultured fibroblasts or isolated leukocytes. Demonstration of normal activity of a different sulfatase enzyme is required to rule out multiple sulfatase deficiency. Urine glycosaminoglycan evaluation can be performed using a variety of

qualitative or quantitative methods to assist in establishing the likelihood of MPS VI but it does not provide a definitive diagnosis.

Historically, supportive therapies and stem cell transplant were the specific therapies available for MPS VI patients. Enzyme replacement therapy with galsulfase has been accepted as a safer option and shown to improve walking and stair-climbing capacity and to decrease urine glycosaminoglycan levels in patients. Reviews and guidelines recommend treatment with galsulfase in patients with MPS VI. Australian guidelines require demonstration of enzyme deficiency in white blood cells in skin fibroblasts or by mutation status in the arylsulfatase B gene. Patients must also present with one of the following: sleep apnea of >5 events/hour (>1 event/hour for children) of total sleep time or 2 episodes of severe oxygen desaturation (mean nocturnal O2 saturation of <85% in adults; <92% in children) during a sleep study; forced vital capacity <80% predicted; decreased ejection fraction <56% [normal range 56-78%] or a decrease in fraction shortening of <25% [normal range 25-46%]; restricted range of motion of joints of >10º; or age < 5 years. Continuation of therapy requires clinical improvement or stabilization of patient's condition.

Morquio A Syndrome[33-35,38-39]

Morquio A Syndrome is also known as Mucopolysaccharidosis Type IVA (MPS IVA). Patients with MPS IVA are deficient in N-acetylgalactosamine 6-sulfatase (GALNS). Without this enzyme glycosaminoglycans keratan sulfate and chondroitin-6-sulfatase accumulate in cell lysosomes which leads to dysfunction in tissues and organs.

Like most of the other MPS phenotypes, MPS IVA is inherited in an autosomal recessive fashion. It is a chronic progressive disease with multisystem involvement (musculoskeletal, respiratory, and cardiovascular, and digestive systems). Examples include valvular heart disease, hepatosplenomegaly impaired vision, depressed respiration, hearing loss and chronic constipation/diarrhea. Morquio syndrome patients do not have the course facial features or mental retardation often seen in the other MPSs. Another distinguishing feature is the additional skeletal and joint issues (unique spondyloepiphyseal dysplasia and ligamentous laxity). These patients tend to have more significant spine involvement (scoliosis, kyphosis, severe gibbus, rib flaring, pectus carinatum) as well as odontoid hypoplasia, short trunk dwarfism, and genu valgus. Odontoid hypoplasia is the most critical skeletal feature to recognize in patients with Morquio syndrome. Odontoid dysplasia and atlantoaxial instability are known to cause cord compression resulting in depressed respiration or sudden respiratory arrest. Reduced growth and final height are associated with more severe clinical phenotypes and increased relative weight is also associated with increased morbidity.

Diagnosis is confirmed by direct enzymatic assay in leukocytes or fibroblasts. The enzymes deficient in Morquio syndrome are galactosamine-6-sulfatase and β-galactosidase. When enzyme activity analysis in fibroblasts or leukocytes is inconclusive, the test should be repeated and/or genetic analysis should be performed. In these cases with inconclusive enzyme results, identification of two known pathogenic mutations on separate alleles is required for definitive diagnosis.

Elosulfase is the currently the only FDA approved agent to treat Morquio A syndrome. Historically only palliative care was available. International guidelines indicate that treatment with elosulfase

alfa should be implemented as soon as the diagnosis of Morquio A syndrome has been confirmed to replace the deficient GALNs enzyme and to help prevent irreversible damage.

Mucopolysaccharidosis VII[47,51-52]
Mucopolysaccharidosis VII (MPS VII), also known as Sly syndrome, is an autosomal recessive disorder caused by mutations in the gene encoding beta-glucronidase (GUSB). The enzyme deficiency results in accumulation of heparan sulfate, dermatan sulfate, chondroitin-4-sulfate, and chrondroitin-6-sulfate. Sly syndrome is extremely rare, affecting about 1 in 250,00 births. Males and females are equally affected.

Clinical features and complications may be similar to Mucopolysaccharidosis I, with significant soft tissue and skeletal abnormalities. Mental retardation may be mild or absent. Hydrops fetalis is a common presentation and may account for a large proportion of patients not being diagnosed due to death before a diagnosis can be made. The most attenuated form is limited to skeletal abnormalities.

In 2017 an enzyme replacement therapy (ERT), Mepsevii (vestronidase alfa-jvbk) was approved to treat pediatric and adult patients with MPS VII. Other treatments of MPS VII are symptomatic and supportive. Bone deformities, hernias, ocular abnormalities, and cardiovascular abnormalities may require surgical correction. The clinical benefits of ERT include decreased hepatomegaly, improved respiratory function, improved walking ability, increased joint range of motion, decreased left ventricular hypertrophy, improved growth, and improved quality of life.

Pompe Disease[12-14,31,37]
Pompe disease [also known as acid maltase deficiency (AMD) or glycogen storage disease type II (GSDII)] is a glycogen and lysosomal storage disease caused by a deficiency of the lysosomal enzyme acid-α-glucosidase (GAA). Symptom onset has great variability and severity depends on the rate of progression and degree of organ involvement. Diagnosis involves several factors including muscle biopsy, electromyelography, ischemic forearm test, creatine kinase levels, history and physical. Assay for enzyme activity revealing deficiency of acid maltase in fibroblasts provides a definitive diagnosis. Pompe disease represents about 15% of all glycogen storage diseases in combined European and American data.

In the infantile presentation, accumulation of glycogen resulting from the inability to convert glycogen to glucose-6-phosphate in cardiac tissue leads to cardiac failure. This form is usually fatal within the first year of life and presents with hypotonia and feeding difficulties. Later onset of disease is associated with more benign symptoms and disease progression with significant morbidity due to respiratory insufficiency due to weakening of respiratory muscles. A high protein diet may be beneficial in the late onset form potentially slowing disease progression and increasing muscle function and exercise tolerance.

There is no specific treatment, but ERT (alglucosidase) may reduce morbidity and prevent complications. According to guidelines, ERT is recommended in patients at the onset of symptoms including proximal muscle weakness and reductions in forced vital air capacity. Patients should be evaluated for efficacy of ERT annually and monitored for IgG antibodies every 3 months for 2 years and annually thereafter.

Australian guidelines for infantile onset Pompe disease require patients to have a diagnosis of deficiency of acid alpha-glucosidase by prenatal diagnosis via chorionic villus biopsies and/or cultured amniotic cells or confirmed diagnosis using 2 of the following dried blot spot enzyme assay, skin fibroblast enzyme assay, lymphocytes, mixed leukocytes, urinary tetrasaccharides, molecular genetic testing, or skeletal muscle. A report from an international consensus meeting on prompt and reliable laboratory diagnosis of Pompe Disease indicates that gene sequencing is the preferred test to confirm diagnosis as it is routinely available and is less invasive among several other benefits. The finding of two pathogenic mutations in trans in the GAA gene is considered confirmatory. Continuation of therapy requires clinical improvement in the patient or stabilization of the patient's condition. Evaluations include disability index/Pompe Pediatric Evaluation of Disability Inventory (PEDI), gross motor function measure, swallowing assessment, neurological examination, growth assessment, etc. Patients are not allowed ERT therapy if they are on long-term invasive ventilation for respiratory failure prior to starting ERT as this would indicate disease severity beyond benefit from treatment. Other guidelines are supportive of this requirement.

SAFETY:
There are no FDA labeled contraindications for the target agents, however, Aldurazyme, Elaprase, Lumizyme, Mepsevii, and Vimizim all have black box warnings concerning life-threatening anaphylactic reactions. Also, patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to infusion reactions.

In addition, Lumizyme also has a black box warning for infantile-onset Pompe disease patients with compromised cardiac or respiratory functions who may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to fluid overload.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J0180	Injection, agalsidase beta, 1 mg
J0220	Injection, alglucosidase alfa, 10 mg, not otherwise specified
J0221	Injection, alglucosidase alfa, (Lumizyme), 10 mg
J1322	Injection, elosulfase alfa, 1 mg
J1458	Injection, galsulfase, 1 mg
J1743	Injection, idursulfase, 1 mg
J1786	Injection, imiglucerase, 10 units
J1931	Injection, laronidase, 0.1 mg
J2840	Injection, sebelipase alfa, 1 mg
J3060	Injection, taliglucerace alfa, 10 units
J3385	Injection, velaglucerase alfa, 100 units

REVISIONS	
08-01-2015	Policy added to the bcbsks.com web site on 06-23-2015 for an effective date of 08-01-2015.
02-01-2016	Policy published 12-30-2015. Policy effective 02-01-2016.
	In Description section: ▪ Updated Dosing chart
	▪ In Policy section: ▪ In **Gauchers Disease** Initial Criteria removed "There is documentation that the patient is already being treated with the requested agent" ▪ In Item 1 A added "There is documentation that the patient is already being treated with the requested agent AND the following: The prescriber has documented current levels of the following: hemoglobin levels, platelet count, liver and spleen volumes, status of bone pain, and if applicable patient's growth velocity" ▪ In Item B added "and ALL of the following:" ▪ In Item I a updated anemia criteria to current language from: "Anemia defined as mean hemoglobin (Hb) of <12.0 g/dL in males > 12 years of age and <11.0 g/dL for females > 12 years of age; Hb < 10.5 g/dL for children > 2 but < 12 years; Hb < 9.5 g/dL for children >6 months and < 2 years and < 10.1 g/dL for children < 6 months" ▪ In Item I f added "(growth velocity below the standard mean for age)" ▪ In Item I g added "other causes ruled out" and removed "Neurologic symptoms consistent" and "disease (e.g. seizures, abnormal ocular movements)" to read "Neurologic symptoms consistent with other causes ruled out disease (e.g. seizures, abnormal ocular movements)" ▪ In Item II added "If the client has a preferred agent, then" ▪ Added Item C C. Genetic analysis with disease causing mutations on 2 alleles of glucocerebrosidase genome and ALL of the following: I. ONE of the following: a. Anemia defined as mean hemoglobin (Hb) of: i. 12 years of age and older: 1. Male: <12.0 g/dL 2. Female: <11.0 g/dL ii. 2 years of age to <12 years of age: < 10.5 g/dL iii. 6 months to <2 years of age: < 9.5 g/dL iv. < 6 months < 10.1 g/dL b. Platelet count of < 100,000/µL on at least 2 measurements c. Liver mass > 1.25 times the normal 2.5% of total body weight d. Splenic mass > the normal 2% of total body weight in kg e. Growth failure (growth velocity below the standard mean for age) f. Evidence of bone disease with other causes ruled out AND II. If the client has a preferred agent, then ONE of the following: a. The patient has tried the preferred agent b. The patient has a documented intolerance, FDA labeled contraindication or hypersensitivity to the preferred agent" ▪ Added Item 2 "The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent" ▪ In Gauchers Disease Renewal Criteria removed "The patient has not experienced a life threatening infusion related reaction that was unable to be controlled by pretreatment with antihistamine, corticosteroids, and adjustments in infusion times" ▪ In Item 2 removed "crisis" and added "disease" ▪ Added Item 3 "The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent" ▪ In **Pompe Disease** Initial Criteria 1 B ii added "Genetic testing confirming two pathogenic mutations on separate alleles in the GAA gene" ▪ In Item 1 B iii removed "molecular genetic testing" and added "biopsy" ▪ Added Items 4 and 5 "4. The prescriber has evaluated current status of one or more of the following: A. Gross motor function (e.g. PEDI-Pompe scale)

REVISIONS	
	B. Swallowing (e.g. videofluoroscopy) C. Neurological function D. Pulmonary function (e.g. FVC % predicted) E. Liver or spleen volumes F. Growth (if applicable) G. Cardiac function (e.g. cardiomyopathy) AND 5. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent" ▪ In Pompe Renewal Criteria removed "The patient has not experienced a life threatening infusion related reaction that was unable to be controlled by pretreatment with antihistamine, corticosteroids, and adjustments in infusion times" ▪ In Item 2 c removed "assessments" and added "function" ▪ In Item 2 g removed "cardiomyopathy" and added "Cardiac function" ▪ Added Item 4 "The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent" ▪ In **Hunter Syndrome** Initial Criteria Item 1 A I added "The prescriber has documented current levels for joint mobility, walking capacity, ejection fraction, forced vital capacity, liver and spleen volume, (and if applicable sleep apnea/desaturation sleep study results)" ▪ In Item 1 B ii 1 removed "in overnight sleep study" and added "In an overnight sleep study the patient has had either an average", "(> apnea event per hour for children) over the patient's" and "(mean nocturnal O2 saturation of <85% in adults; <92% in children)" to read "In an overnight sleep study the patient has had either an average of > 5 apnea events per hour (> apnea event per hour for children) over the patient's total sleep or more than 2 severe episodes of desaturation (mean nocturnal O2 saturation of <85% in adults; <92% in children)" ▪ In Item 1 B ii added "6. Liver mass > 1.25 times the normal 2.5% of total body weight 7. Splenic mass > the normal 2% of total body weight in kg" ▪ Added Item C "C. Genetic analysis of disease causing mutation of the iduronate 2-sulfatase gene and BOTH of the following: i. The patient has normal enzyme activity in at least one other sulfatase enzyme AND ii. ONE of the following: 1. In an overnight sleep study the patient has had either an average of >5 apnea events per hour (>1 apnea event per hour for children) over the patient's total sleep or more than 2 severe episodes of desaturation (mean nocturnal O2 saturation of <85% in adults; <92% in children) 2. Forced vital capacity (FVC) < 80% predicted value for height 3. Reduced ejection fraction of <56% [normal range 56-78%] 4. Reduction in fraction shortening to <25% [normal range 25-46%] 5. Restricted range of movement in joints of > 10◦ from normal 6. Liver mass > 1.25 times the normal 2.5% of total body weight 7. Splenic mass > the normal 2% of total body weight in kg" ▪ Added Item 2 "2. The dose is within the patient does not have any FDA labeled dose contraindication(s) to therapy with the requested agent" ▪ In Hunter Syndrome Renewal Criteria removed "The patient has not experienced a life threatening infusion related reaction that was unable to be controlled by pretreatment with antihistamine, corticosteroids, and adjustments in infusion times" ▪ In Item 2 removed "splenomegaly" and added "f. Liver or spleen volume g. Sleep apnea/severity of desaturation episodes" ▪ Added Item 3 "The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent" ▪ In **Fabry Disease** Initial Criteria Item 1 A added "AND the prescriber has documented current levels of the following: kidney function (Proteinuria, GFR) Cardiac function (Left ventricular hypertrophy, Conduction or rhythm, Mitral or aortic insufficiency), Optic neuropathy, Neuropathic pain, and Gastrointestinal symptoms" ▪ In Item 1 B added "is male and" and "and ALL of the following" and removed "If female, diagnosis is based on mutation of the GAL gene" ▪ Added Item 1 C

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	"C. The patient is female and has a diagnosis based on mutation of the alpha-GAL A gene and ALL of the following: I. ONE of the following: a. Decreased glomerular filtration rate (GFR) as calculated by either CKD-EPI, new Schwartz or Counahan-Barrett formulas OR b. Idiopathic proteinuria of 500 mg/day/1.73 m2 or greater AND II. ONE of the following: a. Left ventricular hypertrophy OR b. Conduction or rhythm abnormalities OR c. Severe mitral or aortic insufficiency AND III. ONE of the following: a. Stroke or TIA as documented by a neurologist OR b. Sudden onset of unilateral hearing loss OR c. Acute ischemic optic neuropathy AND IV. ONE of the following: a. Neuropathic pain that is not responsive to analgesics or opioids OR b. Clinically significant gastrointestinal symptoms for > 6 months not responsive to standard therapies (e.g. metoclopramide, ranitidine, proton pump inhibitors)" ▪ Added Item 2 "The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent" ▪ In Fabry Disease Renewal Criteria removed "The patient has not experienced a life threatening infusion related reaction that was unable to be controlled by pretreatment with antihistamine, corticosteroids, and adjustments in infusion times" ▪ Added Item 3 "The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent" ▪ In **Maroteaux-Lamy Syndrome** Initial Criteria Item 1 A I added "The prescriber has documented current levels for joint mobility, walking capacity, ejection fraction, forced vital capacity, liver and spleen volume, (and if applicable sleep apnea/desaturation sleep study results)" ▪ In Item 1 B added "I. The patient has normal enzyme activity in at least one other sulfatase enzyme AND II. ONE of the following: a. In an overnight sleep study the patient has had either an average of >5 apnea events per hour (>1 apnea event per hour for children) over the patient's total sleep or more than 2 severe episodes of desaturation (mean nocturnal O2 saturation of <85% in adults; <92% in children) b. forced vital capacity (FVC) < 80% predicted value for height c. reduced ejection fraction of <56% [normal range 56-78%] d. reduction in fraction shortening to <25% [normal range 25-46%] e. restricted range of movement in joints of > 10◦ from normal f. Splenic mass > the normal 2% of total body weight in kg g. Liver mass > 1.25 times the normal 2.5% of total body weight" ▪ In Item 1 C II a removed "in overnight sleep study" and added "In an overnight sleep study the patient has had either an average", "(> apnea event per hour for children) over the patient's" and "(mean nocturnal O2 saturation of <85% in adults; <92% in children)" to read "In an overnight sleep study the patient has had either an average of > 5 apnea events per hour (> apnea event per hour for children) over the patient's total sleep or more than 2 severe episodes of desaturation (mean nocturnal O2 saturation of <85% in adults; <92% in children)" ▪ Added Item 2 "The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent" ▪ In Maroteaux-Lamy Syndrome Renewal Criteria removed "The patient has not experienced a life threatening infusion related reaction that was unable to be controlled by pretreatment with antihistamine, corticosteroids, and adjustments in infusion times" ▪ In Item 2 removed "splenomegaly" and added "f. Liver or spleen volume g. Sleep apnea/severity of desaturation episodes" ▪ Added Item 3 "The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent"

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	▪ In **Hurler and Hurler-Scheie, and Sheie Syndrome** Initial Criteria Item 1 A I added "The prescriber has documented current levels for joint mobility, walking capacity, ejection fraction, forced vital capacity, liver and spleen volume, (and if applicable sleep apnea/desaturation sleep study results)" ▪ In Item 1 B added "I. The patient has normal enzyme activity in at least one other sulfatase enzyme AND II. ONE of the following: a. In an overnight sleep study the patient has had either an average of >5 apnea events per hour (>1 apnea event per hour for children) over the patient's total sleep or more than 2 severe episodes of desaturation (mean nocturnal O2 saturation of <85% in adults; <92% in children) b. Forced vital capacity (FVC) < 80% predicted value for height c. Reduced ejection fraction of <56% [normal range 56-78%] d. Reduction in fraction shortening to <25% [normal range 25-46%] e. Restricted range of movement in joints of > 10◦ from normal f. Liver mass > 1.25 times the normal 2.5% of total body weight g. Splenic mass > the normal 2% of total body weight in kg" ▪ In Item 1 c ii A removed "in overnight sleep study" and added "In an overnight sleep study the patient has had either an average", "(> apnea event per hour for children) over the patient's" and "(mean nocturnal O2 saturation of <85% in adults; <92% in children)" to read "In an overnight sleep study the patient has had either an average of > 5 apnea events per hour (> apnea event per hour for children) over the patient's total sleep or more than 2 severe episodes of desaturation (mean nocturnal O2 saturation of <85% in adults; <92% in children)" ▪ In Item 1 c II added "f. Liver mass > 1.25 times the normal 2.5% of total body weight g. Splenic mass > the normal 2% of total body weight in kg" ▪ Added Item 2 "The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent" ▪ In Hurler and Hurler-Scheie, and Sheie Syndrome Renewal Criteria removed "The patient has not experienced a life threatening infusion related reaction that was unable to be controlled by pretreatment with antihistamine, corticosteroids, and adjustments in infusion times" ▪ In Item 2 removed "splenomegaly" and added "f. Liver or spleen volume g. Sleep apnea/severity of desaturation episodes" ▪ Added Item 3 "The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent" ▪ In **Morque A Syndrome** Initial Criteria added "and Renewal" to combine "Initial and Renewal Criteria" ▪ In Item 1 removed "The patient's baseline 6MWT is > 30 meters but < 325 meters" ▪ Added Item 2 'The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent" ▪ Removed Renewal Criteria "1. The patient has been previously approved for therapy through Prime Therapeutics Medical Drug Review process AND 2. The patient has not experienced a life threatening infusion related reaction that was unable to be controlled by pretreatment with antihistamine, corticosteroids, and adjustments in infusion times AND 3. The patient has shown improvement from baseline in distance walked in 6 minutes (6MWT) AND 4. The dose is within the FDA labeled dose" ▪ In Length of Approval revised from "6 months" to "12 months"
	Rationale section updated
	References updated
08-01-2016	Policy published 07-01-2016. Policy effective 08-01-2016.
	Description section updated to add new drug, Kanuma (sebelipase alfa) with update to FDA Approved Indications and Dosage chart.
	In Policy section: ▪ In Renewal Criteria Item 2 for Gaucher's Disease, Hunter Syndrome, Fabry Disease, Maroteaux-Lamy Syndrome, and Hurler Hurler-Scheie, and Sheie Syndrome added "at least" to read "The patient has shown improvement in or stabilization of at least ONE of the following:" ▪ In Pompe Disease, Renewal Criteria, Item 2 added "at least" and remove "or more" to read "The patient has shown improvement in or stabilization of at least ONE of the following:"

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	▪ In Fabry Disease Renewal Criteria added "Length of Approval: 12 months" ▪ Added Initial and Renewal Criteria for new drug: "Lysosomal Acid Lipase Deficiency (LAL-D) Kanuma (sebelipase alfa) Initial Criteria The above referenced agent will be approved when the following are met: 1. ONE of the following: A. There is documentation that the patient is already being treated with the requested agent OR B. The patient has a Lysosomal Acid Lipase Deficiency (LAL-D) as diagnosed by ONE of the following: i. Dried Blood Spot (DBS) testing OR ii. Genetic analysis with the disease causing mutations on the LIPA gene OR iii. Measurement of lysosomal acid lipase activity in peripheral blood mononuclear cells or cultured fibroblasts AND 2. The prescriber has documented current levels of growth (if applicable), lipid levels (ALT, AST, LDL-c, TG, non-HDL-c, HDL-c), and liver volume AND 3. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent AND 4. The dose is within the FDA labeled dose Length of approval: 12 months Renewal Criteria 1. The patient has been previously approved for therapy through Prime Therapeutics Medical Drug Review process AND 2. The patient has shown improvement in or stabilization of at least ONE of the following: i. Growth ii. Lipid levels (ALT, AST, LDL-c, TG, non-HDL-c, HDL-c) iii. Liver volume AND 3. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent AND 4. The dose is within the FDA labeled dose Length of approval: 12 months" ▪ Updated Contraindications chart with new drug "Kanuma (sebelipase alfa)"
	Rationale section updated
	In Coding section ▪ Added HCPCS Code: J3490
	References updated
01-01-2017	Policy published 01-06-2017. Policy effective 01-01-2017.
	In Coding section: ▪ Added HCPCS Code: J2840 (Effective January 1, 2017) ▪ Removed HCPCS Code: J3490 (Effective December 31, 2016)
07-15-2017	Policy published 06-15-2017. Policy effective 07-15-2017.
	Description section updated to remove Myozyme (alglucosidase) from Target Drugs and FDA Approved Indications and Dosage chart.
	In Policy section: <u>Gaucher Disease</u> ▪ In Item 1 B added "or other nucleated cells" to read "The patient has glucocerebrosidase activity of <15% of mean normal in fibroblasts or leukocytes, or other nucleated cells and ALL of the following:" ▪ In Item B I a and C I a revised anemia definition to "Anemia defined as mean hemoglobin (Hb) level below the testing laboratory's lower limit of normal range based on age and gender" from "Anemia defined as mean hemoglobin (Hb) of: i. 12 years of age and older: ii. Male: <12.0 g/dL iii. Female: <11.0 g/dL iv. 2 years of age to <12 years of age: < 10.5 g/dL v. 6 months to <2 years of age: <9.5 g/dL vi. <6 months <10.1 g/dL" <u>Pompe Disease</u> ▪ Removed Myozyme (alglucosidase)

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	▪ Removed "If the requested agent is Myozyme, the patient has infantile onset disease" Hunter Syndrome (Mucopolysaccharidosis type II [MPS II]) ▪ In Item C removed "The patient has normal enzyme activity in at least one other sulfatase enzyme" Fabry Disease ▪ Removed "ONE of the following: a. Decreased glomerular filtration rate (GFR) as calculated by either CKD-EPI, new Schwartz or Counahan-Barrett formulas OR b. Idiopathic proteinuria of 500 mg/day/1.73 m2 or greater AND II. ONE of the following: a. Left ventricular hypertrophy OR b. Conduction or rhythm abnormalities OR c. Severe mitral or aortic insufficiency AND III. ONE of the following: a. Stroke or TIA as documented by a neurologist OR b. Sudden onset of unilateral hearing loss OR c. Acute ischemic optic neuropathy AND IV. ONE of the following: a. Neuropathic pain that is not responsive to analgesics or opioids OR b. Clinically significant gastrointestinal symptoms for > 6 months not responsive to standard therapies (e.g. metoclopramide, ranitidine, proton pump inhibitors)" Maroteaux-Lamy Syndrome (Mucopolysaccharidosis type VI [MPS VI]) ▪ In Item C removed "The patient has normal enzyme activity in at least one other sulfatase enzyme" Hurler Hurler-Scheie, and Sheie Syndrome (Mucopolysaccharidosis type I [MPS I]) ▪ In Item C removed "The patient has normal enzyme activity in at least one other sulfatase enzyme" Lysosomal Acid Lipase Deficiency (LAL-D) ▪ In Item B removed "BOTH of the following: 1. If the patient has the cholesteryl ester storage disease variant (CESD), then the patient has failed maximally tolerated statin therapy OR 2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to all statins" ▪ In Initial Evaluation Item 2 and Renewal Criteria 2 ii "removed "ALT, AST" from lipid level to read "Lipid levels (LDL-c, TG, non-HDL-c, HDL-c) ▪ Updated contraindications chart by removing Myozyme (alglucosidase). ▪ Throughout the policy language section corrected Splenic mass definition to "> the normal 0.2% of total body weight in kg" from "> the normal 2% of total body weight in kg"
	Rationale section updated
	References updated
06-15-2018	Description section updated: ▪ Added Mepsevii (vestronidase alfa-vjbk) to the Target Agents and FDA Approved Indications and Dosage charts.
	In Policy section: The policy revisions are in summary: • Separated Gaucher Disease initial criteria (1) into 2 bullet points for clarity • Separated Hunter Syndrome initial criteria (1) into 2 bullet points for clarity • Separated Maroteaux-Lamy Sendrome initial criteria (1) into 2 bullet points for clarity • Separated Hurler, Hurler-Scheie, and Scheie Syndrome initial criteria (1) into 2 bullet points for clarity • Added requirement that prescriber has documented the current walking capacity in Morquio A Syndrome initial criteria • Added Morquio A Syndrome renewal criteria • Added clarification of needing specific diagnosis vs accepting only lab tests • Added requirement of the patient is seeing a specialist or the prescriber is a specialist to all agents before allowing for approval • Added requirement for Eyelyso and Vpriv that patient is 4 years old or older per labeling • Added Mepsevii for treatment of MPS VII
	Gaucher Disease Initial Evaluation ▪ In Item 1 added "B. The patient has a diagnosis of Gaucher disease Type 1 and ALL of the following:

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	i. The patient does NOT have any neuropathic symptoms [e.g. convulsive crisis, ataxia, supranuclear horizontal ocular palsy, dementia, alteration in ocular movement, bulbar (swallowing difficulties, stridor, convergent strabismus)] AND ii. If the requested agent is Eleyso or Vpriv, the patient is 4 years old or older AND iii. ONE of the following 1. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist) OR 2. The prescriber has consulted with a specialist in the area of practice realted to the patient's diagnosis" ▪ In Item 1 B iv added, "2. The patient has genetic analysis with disease causing mutations on 2 alleles of glucocerebrosidase genome" ▪ Removed the following: "C. Genetic analysis with disease causing mutations on 2 alleles of glucocerebrosidase genome and ALL of the following: I. ONE of the following: a. Anemia defined as mean hemoglobin (Hb) level below the testing laboratory's lower limit of normal range based on age and gender OR b. Platelet count of < 100,000/µL on at least 2 measurements OR c. Liver mass > 1.25 times the normal 2.5% of total body weight OR d. Splenic mass > the normal 0.2% of total body weight in kg OR e. Growth failure (growth velocity below the standard mean for age) OR f. Evidence of bone disease with other causes ruled out AND II. If the client has a preferred agent, then ONE of the following: a. The patient has tried the preferred agent OR b. The patient has a documented intolerance, FDA labeled contraindication or hypersensitivity to the preferred agent" <u>Pompe Disease and Lysosomal Acid Lipase Deficiency (LAL-D) Initial Evaluation</u> ▪ In Item 1 B added "1. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist) OR 2. The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis" <u>Hunter Syndrome [Mucopolysaccharidosis type II (MPS II)] Initial Evaluation</u> ▪ To Item 1 B i "2. The patient has genetic analysis of disease causing mutation of the iduronate 2-sulfatase gene AND ii. ONE of the following: 1. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist) OR 2. The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis" ▪ Removed the following: "Genetic analysis of disease causing mutation of the iduronate 2-sulfatase gene and ONE of the following: i. In an overnight sleep study the patient has had either an average of >5 apnea events per hour (>1 apnea event per hour for children) over the patient's total sleep or more than 2 severe episodes of desaturation (mean nocturnal O2 saturation of <85% in adults; <92% in children) ii. Forced vital capacity (FVC) < 80% predicted value for height iii. Reduced ejection fraction of <56% [normal range 56-78%] iv. Reduction in fraction shortening to <25% [normal range 25-46%] v. Restricted range of movement in joints of > 10◦ from normal vi. Liver mass > 1.25 times the normal 2.5% of total body weight vii. Splenic mass > the normal 0.2% of total body weight in kg" <u>Fabry Disease Initial Evaluation</u> ▪ In Item 1 B added. "ii. ONE of the following:

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	1. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist) OR 2. The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis" Maroteaux-Lamy Syndrome [Mucopolysaccharidosis type (VI MPS VI)] Initial Evaluation ▪ To Item 1 B added, "2. The patient has genetic analysis of disease causing mutation of the arylsulfatase B gene AND ii. ONE of the following: 1. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist) OR 2. The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis" ▪ Removed the following: "C. Genetic analysis with disease causing mutation in the arylsulfatase B gene and ONE of the following: I. In an overnight sleep study the patient has had either an average of > 5 apnea events per hour (>1 apnea event per hour for children) over the patient's total sleep or more than 2 severe episodes of desaturation (mean nocturnal O2 saturation of <85% in adults; <92% in children) II. Forced vital capacity (FVC) < 80% predicted value for height III. Reduced ejection fraction of <56% [normal range 56-78%] IV. Reduction in fraction shortening to <25% [normal range 25-46%] V. Restricted range of movement in joints of > 10◦ from normal VI. Splenic mass > the normal 0.2% of total body weight in kg VII. Liver mass > 1.25 times the normal 2.5% of total body weight" Hurler Hurler-Scheie, and Sheie Syndrome (Mucopolysaccharidosis type I [MPS I]) Initial Evaluation ▪ Added to Item B "2. The patient has genetic analysis of disease causing mutation of the arylsulfatase B gene AND ii. ONE of the following: 1. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist) OR 2. The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis" ▪ Removed the following: "C. Genetic analysis with disease causing mutation in the arylsulfatase B gene and ONE of the following: I. In an overnight sleep study the patient has had either an average of > 5 apnea events per hour (>1 apnea event per hour for children) over the patient's total sleep or more than 2 severe episodes of desaturation (mean nocturnal O2 saturation of <85% in adults; <92% in children) II. Forced vital capacity (FVC) < 80% predicted value for height III. Reduced ejection fraction of <56% [normal range 56-78%] IV. Reduction in fraction shortening to <25% [normal range 25-46%] V. Restricted range of movement in joints of > 10◦ from normal VI. Splenic mass > the normal 0.2% of total body weight in kg VII. Liver mass > 1.25 times the normal 2.5% of total body weight" Gaucher Disease; Pompe Disease, Hunter Syndrome [Mucopolysaccharidosis type II (MPS II)]; Fabry Disease; Maroteaux-Lamy Syndrome [Mucopolysaccharidosis type (VI MPS VI)]; Hurler Hurler-Scheie, and Sheie Syndrome (Mucopolysaccharidosis type I [MPS I]); Lysosomal Acid Lipase Deficiency (LAL-D) Renewal Evaluation ▪ Added "2. ONE of the following: A. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist) OR B. The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis" Morque A Syndrome [Mucopolysaccharidosis type IVA (MPS IVA)] Initial and Renewal Evaluation ▪ Separated Initial and Renewal Evaluation Criteria to be two separate criteria sections. "Initial Evaluation

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	Vimizim will be approved when ALL of the following are met: 1. ONE of the following: A. There is documentation that the patient is already being treated with the requested agent OR B. The patient has a diagnosis of Morquio A Syndrome [Mucopolysaccharidosis type IVA (MPS IVA)] and BOTH of the following: i. The patient has a N-acetylgalactosamine 6-sulfatase (GALNS) deficiency as diagnosed by ONE of the following: 1. Prenatal diagnosis via chorionic villus biopsies and/or cultured amniotic cells OR 2. The patient has a N-acetylgalactosamine 6-sulfatase (GALNS) deficiency in leukocytes or fibroblasts OR 3. Genetic analysis with disease causing mutation of the N-acetylgalactosamine 6-sulfatase (GALNS) gene AND ii. ONE of the following: 1. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist) OR 2. The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis AND 2. The prescriber has documented the current walking capacity AND 3.The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent AND 4.The dose is within the FDA labeled dose Length of approval: 12 months Renewal Evaluation 1. The patient has been previously approved for therapy through Prime Therapeutics Medical Drug Review process for the requested agent AND 2. ONE of the following: A. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist) OR B. The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis AND 3. The patient has shown improvement in or stabilization in walking capacity AND 4. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent AND 5. The dose is within the FDA labeled dose Length of approval: 12 months" Removed "Initial and Renewal Evaluation Criteria The above referenced agent will be approved when the following are met: 5. ONE of the following: A. There is documentation that the patient is already being treated with the requested agent OR B. The patient has a N-acetylgalactosamine 6-sulfatase (GALNS) deficiency as diagnosed by ONE of the following: i. Prenatal diagnosis via chorionic villus biopsies and/or cultured amniotic cells OR ii. The patient has a N-acetylgalactosamine 6-sulfatase (GALNS) deficiency in leukocytes or fibroblasts OR iii. Genetic analysis with disease causing mutation of the N-acetylgalactosamine 6-sulfatase (GALNS) gene AND 6. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent AND 7. The dose is within the FDA labeled dose Length of approval: 12 months" Mucopolysaccharidosis VII (MPSVII) (Sly syndrome) Initial and Renewal Evaluation ▪ Added new criteria "Initial Evaluation Mepsevii will be approved when ALL of the following are met: 1. ONE of the following: A. BOTH of the following: i. There is documentation that the patient is already being treated with the requested agent AND

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	ii. The prescriber has documented current levels for joint mobility, walking capacity, ejection fraction, forced vital capacity, liver and spleen volume, (and if applicable sleep apnea/desaturation sleep study results) OR B. The patient has a diagnosis of Sly Syndrome [mucopolysaccharidosis type VII (MPS VII)] and ALL of the following: i. ONE of the following: 1. The patient has a beta-glucuronidase deficiency in leukocytes, fibroblasts, or plasma OR 2. The patient has genetic analysis of disease causing mutation of the beta-glucuronidase gene AND ii. ONE of the following: 1. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist) OR 2. The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis AND iii. ONE of the following: 1. In an overnight sleep study the patient has had either an average of >5 apnea events per hour (>1 apnea event per hour for children) over the patient's total sleep OR more than 2 severe episodes of desaturation (mean nocturnal O2 saturation of <85% in adults; <92% in children) OR 2. The patient has a forced vital capacity (FVC) < 80% predicted value for height OR 3. The patient has reduced ejection fraction of <56% [normal range 56-78%] OR 4. The patient has a reduction in fraction shortening to <25% [normal range 25-46%] OR 5. The patient has restricted range of movement in joints of > 10◦ from normal OR 6. The patient has hepatomegaly OR 7. The patient has splenomegaly AND 2. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent AND 3. The dose is within the FDA labeled dose Length of Approval: 12 months Renewal Evaluation 1. The patient has been previously approved for therapy through Prime Therapeutics Medical Drug Review process for the requested agent AND 2. ONE of the following: A. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. endocrinologist, geneticist) OR B. The prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis AND 3. The patient has shown improvement in or stabilization of at least ONE of the following: A. Joint mobility OR B. Walking capacity OR C. Ejection fraction OR D. Fraction shortening OR E. Forced vital capacity OR F. Liver or spleen volume OR G. Sleep apnea/severity of desaturation episodes AND 4. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent AND 5. The dose is within the FDA labeled dose Length of Approval: 12 months" ▪ Updated Contraindications chart.
	Rationale section updated
	References updated

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