Effective Date: 5/3/2018

Adagen® (pegademase bovine)
Aldurazyme® (laronidase)
Brineura™ (cerliponase alfa)
Cerezyme® (imiglucerase)
Elaprase® (idursulfase)
Elelyso® (taliglucerase)
Fabrazyme® (agalsidase beta)
Kanuma™ (sebelipase alfa)
Lumizyme® (alglucosidase alfa)
Mepsevii™ (vestronidase alfa-vjbk)
Myozyme® (alglucosidase alfa)
Naglazyme® (galsulfase)
Strensiq™ (asfatase alfa)
Vimizim™ (elosulfase alfa)
Vpriv® (velaglucerase alfa)

FDA approval: See Table 1
HCPCS: See Table 1
Benefit: Both Pharmacy and Medical, see Table 1 for specifics

Policy/Criteria:

Note: Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the below criteria are met:
   a) Type 1 Gaucher (Cerezyme, Elelyso, Vpriv)
      i. Diagnosis must be made by or in consultation with a geneticist or metabolic specialist
      ii. Diagnosis of Type 1 Gaucher disease confirmed by one of the following:
          1. Biochemical assay of glucocerebrosidase activity in WBCs or skin fibroblasts is less than
             or equal to 30% of normal activity (Note: laboratory normals may vary) OR
          2. Genotyping revealing two pathogenic mutations of the glucocerebrosidase gene
      iii. Symptomatic manifestations of the disease are present, such as anemia, thrombocytopenia, bone
           disease, hepatomegaly or splenomegaly
      iv. Patient has experienced treatment failure or intolerance to the preferred product
   b) Mucopolysaccharidosis (MPS)
      i. Diagnosis must be made by or in consultation with a geneticist or metabolic specialist
      ii. Baseline disease status must be documented
      iii. MPS I (Aldurazyme)
          1. Diagnosis of Hurler and Hurler-Scheie forms of MPS I OR Scheie form who have
             moderate to severe symptoms (see Appendix 1)
2. Diagnosis must be confirmed by serum assays showing enzyme deficiency of alpha-L-iduronidase AND Urinary glycosaminoglycan (GAG), dermatan sulfate or heparin sulfate

iv. MPS II *(Elaprase)*
   1. Diagnosis of Hunter’s Syndrome (MPS II)
   2. Diagnosis must be confirmed by serum assays of enzyme deficiency of iduronate sulfatase AND Urinary GAG, dermatan sulfate or heparin sulfate

v. MPS IVA *(Vimizim)*
   1. 5 years of age or older AND
   2. Diagnosis of MPS IVA (Morquio A syndrome)
   3. Diagnosis must be confirmed by serum assays of enzyme deficiency of N-acetylglucosamine-6-sulfatase, AND Urinary GAG keratin sulfate

vi. MPS VI *(Naglazyme)*
   1. Diagnosis of MPS VI.
   2. Diagnosis must be confirmed by serum assays of enzyme deficiency of N-acetylglucosamine-6-sulfatase, AND Urinary GAG dermatan sulfate

vii. MPS VII *(Mepsevii)*
   1. Diagnosis of MPS VII (Sly syndrome).
   2. Diagnosis must be confirmed by serum assays showing enzyme deficiency of beta-glucuronidase AND Urinary glycosaminoglycan (GAG), dermatan sulfate, heparan sulfate, or chondroitin sulfate.

  c) Fabry Disease *(Fabrazyme)*
   i. Diagnosis must be made by or in consultation with a geneticist or metabolic specialist
   ii. Diagnosis of Fabry Disease
      1. All other conditions (such as cardioembolic stroke, or dissection syndromes) have been ruled out
      2. Diagnosis of males must show deficient activity of the enzyme α-galactosidase in plasma and/or leukocytes AND molecular genetic testing of GLA mutation
      3. Diagnosis of females must include molecular genetic testing of GLA mutation
   iii. Must show clinical manifestations of disease (kidney dysfunction, severe pain in the extremities, etc.) and provide baseline kidney, nervous system, and heart function as well overview of patient’s quality of life
   iv. Must provide goals of therapy

d) Pompe Disease
   i. Diagnosis must be made by or in consultation with a geneticist or metabolic specialist
   ii. Diagnosis of infantile-onset Pompe disease. *(Myozyme or Lumizyme)*
      1. All other conditions (such as hypothyroidism or myocarditis) have been ruled out
      2. Diagnosis has been confirmed by the absence of GAA (acid alpha glucosidase) activity (via GAA mutation testing or GAA activity testing in fibroblasts or muscle) AND
      3. Diagnosis is supported by a series of screening tests including chest x-ray, electrocardiogram (ECG), electromyogram (EMG), and/or creatine kinase (CK) among other laboratory tests
   iii. Diagnosis of late-onset (non-infantile) Pompe disease and do not have evidence of cardiac hypertrophy. *(Lumizyme)*
      1. A Diagnosis must be made by or in consultation with a geneticist or metabolic specialist
         a. All other conditions (such as Polymyositis or Rheumatoid Arthritis) have been ruled out
         b. Diagnosis has been confirmed by the reduced activity of GAA (acid alpha glucosidase) activity (via GAA mutation testing or GAA activity testing in fibroblasts or muscle) AND
         c. Diagnosis is supported by a series of screening tests including chest x-ray, electrocardiogram (ECG), electromyogram (EMG), and/or creatine kinase (CK) among other laboratory tests.

e) Adenosine Deaminase Deficiency (Severe Combined Immunodeficiency) *(Adagen)*

This policy and any information contained herein is the property of Blue Cross Blue Shield of Michigan and its subsidiaries, is strictly confidential, and its use is intended for the P&T committee, its members and BCBSM employees for the purpose of coverage determinations.
i. Diagnosis must be made by or in consultation with an immune specialist
ii. Diagnosis of adenosine deaminase (ADA) deficiency in patients with severe combined immunodeficiency disease (SCID)
iii. Diagnosis confirmed by evidence of combined immunodeficiency (very low T, B, and NK lymphocyte counts) AND an absence of thymus and other lymphoid tissues
iv. Have tried and failed or found to not be a suitable candidate (for example, unable to find donor) for bone marrow transplantation.
v. AND does not have severe thrombocytopenia

f) Lysosomal acid lipase deficiency (LAL-d) (Kanuma)
i. Diagnosis must be made by or in consultation with a geneticist or metabolic specialist
ii. Diagnosis of LAL-d confirmed by blood test measuring LAL activity OR genetic testing
iii. Symptomatic manifestations of the disease are present such as, elevated liver enzymes, microvesicular steatosis, elevated low-density lipoprotein, low high-density lipoprotein, or coronary artery disease


g) Pediatric-onset hypophosphatasia (HPP) (Strensiq)
i. Patient must be under the age of 18 at onset of symptoms
ii. Diagnosis must be made by or in consultation with a geneticist, metabolic specialist, endocrinologist, or bone and mineral specialist
iii. Diagnosis must be confirmed by all of the following:
   1. Medical history/physical exam
   2. X-ray skeletal alterations
   3. Low serum alkaline phosphatase (ALP) activity confirmed by high substrate levels (PPI, PEA, and PLP)
iv. Must have documentation of active disease manifestations (examples: skeletal malformations/fractures, respiratory difficulties, dental manifestations, kidney damage, and seizures)

h) Late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) (Brineura)
i. Patient must be 3 years of age or older
ii. Diagnosis made by or in consultation with a neurologist, geneticist, or metabolic specialist
iii. Diagnosis must be confirmed by deficiency in tripeptidyl peptidase 1 enzyme OR genetic mutation in CLN2 gene
iv. Patient must be ambulatory at the time of treatment initiation
v. Documentation patient will be on standard of care regimen for CLN2 (e.g. seizure management, nutritional support, physical therapy)

B. Quantity Limitations, Authorization Period and Renewal Criteria
a) Quantity Limit:
i. Cerezyme, Elelyso, Vpriv: Lowest risk patients: 30U/kg every 2 weeks; Increased risk patients: 60U/kg every 2 weeks (please see Appendices 2 and 3)
ii. Aldurazyme: 0.58 mg/kg intravenous (IV) infusion once weekly
iii. Elaprase: 0.5 mg/kg as an IV infusion once a week
iv. Vimizim: 2mg/kg/week with no more than one dose per week.
v. Naglazyme: 1 mg/kg once weekly
vi. Fabrazyme: 1 mg/kg body weight infused every 2 weeks
vii. Mepsevii: 4mg/kg every 2 weeks
viii. Myozyme/Lumizyme: 20 mg/kg body weight administered every 2 weeks
ix. Adagen: 30 units/kg intramuscularly once weekly
x. Kanuma:
   1. Pediatric and adult patients with LAL-d: 1 mg/kg every 2 weeks
   2. Patients < 6 months with rapidly progressive LAL-d: 3 mg/kg once weekly
xi. Strensiq: 2 mg/kg subcutaneously three times a week or 1mg/kg subcutaneously six times a week.
xii. Brineura: 300 mg every other week by intraventricular injection followed by infusion of intraventricular electrolytes over 4.5 hours

This policy and any information contained herein is the property of Blue Cross Blue Shield of Michigan and its subsidiaries, is strictly confidential, and its use is intended for the P&T committee, its members and BCBSM employees for the purpose of coverage determinations.
b) Initial Authorization Period: 6 months

c) Renewal Criteria – must meet initial criteria above AND:
   i. Gaucher Disease (Cerezyme, Elyso, Vpriv)
      1. Documentation showing maintenance or improvement in disease must be provided including assessments of hemoglobin, platelet count, and liver and/or spleen volumes by MRI, if the MRI is clinically indicated
   ii. Mucopolysaccharidosis (Aldurazyme, Elaprase, Vimizim, Naglazyme, Mepsevii)
      1. Patient must have improved or stabilized from baseline disease status
      2. Examples of improvement vary by disease; however they could include improved Quality of Life, decreased hepatosplenomegaly, or decreased urinary GAG levels
   iii. Fabry Disease (Fabrazyme)
      1. Documentation that goals of therapy have been met. These goals may include decreases in pain, fatigue OR overall improvement in kidney or cardiovascular function
   iv. Pompe Disease (Myozyme, Lumizyme)
      1. Documentation of patient’s progress of disease status from notes by physician
   v. Adenosine Deaminase Deficiency (Severe Combined Immunodeficiency) (Adagen)
      1. Documentation of patient’s progress of disease status from notes by physician
   vi. Lysosomal Acid Lipase Deficiency (Kanuma)
      1. Documentation showing maintenance or improvement in disease must be provided
      2. Examples of improvement may include (but are not limited to) normal liver enzymes and improved lipid levels
   vii. Hypophosphatasia (Strensiq)
      1. Documentation of response to therapy
      2. Examples of response to therapy may include (but are not limited to) improvement in respiratory status and skeletal structure
   viii. Late infantile neuronal ceroid lipofuscinosis type 2 (Brineura)
      1. Documentation of response to therapy
      2. Currently ambulatory while on therapy

d) Renewal Authorization Period: 1 year

C. Enzyme Replacement Therapy is considered investigational when used for all other conditions, including but not limited to:
   a) Types 2 or 3 Gaucher Disease
   b) Enzyme deficiency other than the N-acetylgalactosamine-6-sulfase (GALNS) enzyme deficiency
   c) Non-ambulatory patients with ventilator dependence
   d) Use in combination with Zavesca for Type 1 Gaucher
   e) Adult-onset HPP for hypophosphatasia
   f) Other forms of Batten Disease
   g) Use for anything other than FDA approved indication

***Note: Coverage may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia

Therapeutic considerations:

A. FDA approved Indication/Diagnosis

<table>
<thead>
<tr>
<th>Drug/Manufacturer</th>
<th>J Codes</th>
<th>Pharmacy/Medical</th>
<th>FDA Indications</th>
</tr>
</thead>
</table>

This policy and any information contained herein is the property of Blue Cross Blue Shield of Michigan and its subsidiaries, is strictly confidential, and its use is intended for the P&T committee, its members and BCBSM employees for the purpose of coverage determinations.
<table>
<thead>
<tr>
<th>Approval Date</th>
<th>Code</th>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
</table>
| Adagen ® March 21, 1990  
*P&T History: Unknown* | J2504      | Medical | Injection is indicated for enzyme replacement therapy (ERT) for adenosine deaminase (ADA) deficiency in patients with severe combined immunodeficiency disease (SCID) who are not suitable candidates for – or who have failed – bone marrow transplantation. |
| Aldurazyme ® April 30, 2003  
*P&T History: Unknown* | J1931      | Medical | Indicated for patients with Hurler and Hurler-Scheie forms of Mucopolysaccharidosis (MPS) I and for patients with the Scheie form who have moderate to severe symptoms. |
| Brineura™ April 27, 2017  
*P&T History: 11/9/2017* | J3490/J3590 | Medical | Indicated to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency. |
| Cerezyme ® May 23, 1994  
*P&T History: Unknown Drug Review/Type 1 Gaucher – 8/9/12* | J1786      | Medical | Indicated for long-term ERT for patients with a confirmed diagnosis of Type 1 Gaucher disease that results in one or more of the following conditions: anemia, thrombocytopenia, bone disease, hepatomegaly or splenomegaly. |
| Elaprase ® July 24, 2006  
*P&T History: 10/26/06* | J1743      | Medical | Indicated for patients with Hunter syndrome (MPS II). |
| Elelyso ® May 1, 2012  
*P&T History: 8/9/12/ Type 1 Gaucher – 8/9/12* | J3060      | Medical | A hydrolytic lysosomal glucocerebrosidase-specific enzyme indicated for long-term ERT for adults and children with a confirmed diagnosis of Type 1 Gaucher disease. |
| Fabrazyme ® April 24, 2003  
*P&T History: Unknown* | J0180      | Medical | Indicated for use in patients with Fabry disease. |
| Kanuma™ December 8, 2015  
*P&T History: 5/5/2015* | J2840      | Medical | Indicated for lysosomal acid lipase deficiency |
| Lumizyme ® May 24, 2010  
*P&T History: 7/15/10* | J0221      | Medical | Patients with Pompe Disease (acid α-glucosidase deficiency) |
| Mepsevii™ November 15, 2017  
| Myozyme ® April 28, 2006  
*P&T History: 10/26/06* | J0220      | Medical | Indicated for use in patients with Pompe disease. |
| Naglazyme ® May 31, 2005  
*P&T History: * | J1458      | Medical | Indicated for patients with MPS VI |
**Background Information**

a. ERT is a lifelong therapy that falls under multiple disease state categories. The most common is the lysosomal storage diseases (LSDs) which covers Gaucher disease, Fabry disease, Pompe Disease, LAL-d, and the mucopolysaccharidoses among many others

b. LSDs are genetic diseases defined by the lack of sufficient enzymatic activity (via enzyme deficiency or dysfunction) to prevent the accumulation of specific macromolecules

i. Gaucher Disease
   1. Type 1 Gaucher Disease is the most common of the LSDs (and much more common than Type 2 or 3 Gaucher disease). Onset of symptoms vary from early childhood to late adulthood with early childhood cases typically being the most severe
   2. Signs and symptoms include anemia, hepatosplenomegaly, skeletal disease and sometimes lung or liver impairment

ii. Fabry Disease
   1. Incidence of this condition is estimated at 1 in 50,000 individuals and affects primarily males. Without treatment males typically live to 41-55 years and females about 15 years less than the average life-span of females
   2. Major organ dysfunction can occur in this disease, including the kidney, cardiovascular system and GI tract. Therapy is recommended to start initial prior to obvious organ dysfunction

iii. Pompe Disease (Glycogen Storage Disease Type 2)
   1. Caused by deficiency of alpha-glucosidase resulting in lysosomal glycogen accumulation
   2. Divided into early and late onset forms
   3. Life expectancy in early forms is less than 1 year
   4. Late onset form can occur from childhood into the 60s with primary musculoskeletal involvement

iv. Mucopolysaccharidoses (MPS)
   1. Group of LSDs that result in abnormal tissue accumulations of glycosaminoglycans
   2. There are multiple MPS disorders with 4 of the disorders having enzyme replacement therapy available: MPS I (Hurler, Hurler-Scheie, and Scheie syndrome), MPS II (Hunter Syndrome), MPS VI (Maroteaux-Lamy Syndrome), and MPS VII (Sly Syndrome)
   3. Stem cell or bone marrow transplant (BMT) is the standard of care for patients with severe MPS I (Hurler syndrome) if diagnosed and performed under the age of 2 years old

v. Lysosomal Acid Lipase Deficiency

*Please refer to most recent prescribing information.

[www.fda.gov](http://www.fda.gov)
1. LAL-d is a rare autosomal recessive genetic disease caused by a mutation in the LIPA gene
2. LAL is necessary for cleavage of triglycerides and cholesteryl esters delivered to lysosomes and deficiencies leads to accumulation of esters in vital organs and tissues with subsequent progressive multi-system organ damage with symptoms such as elevated in liver enzymes and changes to the lipid profile that eventually leads to death
3. Two major phenotypes of this condition are Wolman disease, which manifest in infancy, and cholesteryl ester storage disease (CESD)

   c. Adenosine deaminase (ADA) deficiency in a patient with severe combined immunodeficiency disease (SCID):
      i. ADA is a systemic purine metabolic disorder that primarily affects lymphocyte development, viability, and function
      ii. Deficiency is typically shown by very low T, B, and NK lymphocyte counts in peripheral blood and an absence of thymus and other lymphoid tissues
      iii. SCID is most often diagnosed between 6 and 12 months of age, but can have a delayed onset into adulthood

   d. Hypophosphatasia (HPP):
      i. HPP is an inherited metabolic disorder caused by a mutation of the enzyme tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP)
      ii. HPP has an incidence rate of 1 in 100,000 live births. Patients who develop symptoms of HPP by 6 months of age have a mortality rate of over 70% by the age of 5
      iii. Alterations in the TNSALP gene can lead to low alkaline activity levels and ultimately to bone pain and fractures, seizures, respiratory depression, rickets, osteomalacia, or both, which characterize this disorder

   e. Late infantile neuronal ceroid lipofuscinosis type 2 (CLN2)
      i. CLN2 is one of a group of disorders known as neuronal ceroid lipofuscinoses (NCLs) collectively referred to as Batten disease
      ii. The estimated incidence of CLN2 is approximately one in 200,000
      iii. It is a rare inherited disorder caused by a mutation in the CLN2 gene that directs production of the enzyme TPP1.
      iv. CLN2 is a rapidly progressing, fatal disease usually presenting between the ages of 2 to 4 years. Initial symptoms can include language delay and seizures, followed by movement disorders, motor deterioration, dementia and blindness, death often occurs between 8 and 12 years of age.

<table>
<thead>
<tr>
<th>Cross References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vimizim® (elosulfase alfa) 8/14/14</td>
</tr>
<tr>
<td>Elelyso® (taliglucerase alfa) 8/09/12</td>
</tr>
<tr>
<td>Enzyme Replacement Therapy for the Treatment of Gaucher Disease (Cerezyme®, Elelyso™, Vpriv®) 8/09/12</td>
</tr>
<tr>
<td>JUMP Policy – Agalsidase Beta (Fabrazyme) Infusion for Fabry Disease</td>
</tr>
<tr>
<td>Strensiq™ (asfotase alfa) 2/11/2016</td>
</tr>
<tr>
<td>Kanuma™ (sebelipase alfa) 5/5/2016</td>
</tr>
</tbody>
</table>

C. Efficacy

*Please refer to most recent prescribing information.

D. Medication Safety Considerations

This policy and any information contained herein is the property of Blue Cross Blue Shield of Michigan and its subsidiaries, is strictly confidential, and its use is intended for the P&T committee, its members and BCBSM employees for the purpose of coverage determinations.
Boxed Warning: Life threatening anaphylactic reactions, especially for those with compromised respiratory function or acute respiratory disease. (Aldurazyme, Elaprase, and Vimizim)

Life threatening anaphylactic reactions and severe hypersensitivity reactions (Lumizyme, Myozyme)

Infantile-onset Pompe disease patients with compromised cardiac or respiratory function may be at serious risk of acute exacerbation. (Lumizyme, Myozyme)

*Please refer to most recent prescribing information.

E. Dosing and administration

*Please refer to most recent prescribing information.

F. How supplied

*Please refer to most recent prescribing information.

References:


This policy and any information contained herein is the property of Blue Cross Blue Shield of Michigan and its subsidiaries, is strictly confidential, and its use is intended for the P&T committee, its members and BCBSM employees for the purpose of coverage determinations.


Policy History

<table>
<thead>
<tr>
<th>#</th>
<th>Date</th>
<th>Change Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>Effective Date:</td>
<td>New Class Criteria Document</td>
</tr>
</tbody>
</table>

This policy and any information contained herein is the property of Blue Cross Blue Shield of Michigan and its subsidiaries, is strictly confidential, and its use is intended for the P&T committee, its members and BCBSM employees for the purpose of coverage determinations.
<table>
<thead>
<tr>
<th>Date</th>
<th>Effective Date</th>
<th>Updated</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/30/2014</td>
<td></td>
<td>Updated with preliminary UM criteria two new therapies (sebelipase alfa and asfotase alfa)</td>
</tr>
<tr>
<td>1.1</td>
<td>11/05/2015</td>
<td>Updated with newly approved drug Strensiq</td>
</tr>
<tr>
<td>1.2</td>
<td>2/11/2016</td>
<td>Updated with newly approved Kanuma</td>
</tr>
<tr>
<td>1.3</td>
<td>5/5/2016</td>
<td>Annual Review Update</td>
</tr>
<tr>
<td>1.4</td>
<td>5/4/2017</td>
<td>Updated with Brineura</td>
</tr>
<tr>
<td>1.5</td>
<td>11/9/2017</td>
<td>Updated with Mepsevii</td>
</tr>
</tbody>
</table>

*The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or [http://dailymed.nlm.nih.gov/dailymed/index.cfm](http://dailymed.nlm.nih.gov/dailymed/index.cfm)*