TREATMENTS FOR GAUCHER DISEASE

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Medical Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

BLUE CROSS®, BLUE SHIELD® and the Cross and Shield Symbols are registered service marks of the Blue Cross and Blue Shield Association, an association of independent Blue Cross and Blue Shield Plans. All other trademarks and service marks contained in this guideline are the property of their respective owners, which are not affiliated with BCBSAZ.
TREATMENTS FOR GAUCHER DISEASE (cont.)

Description:

Gaucher’s disease is an inherited lysosomal storage disorder that results from the inability to produce the enzyme beta-glucocerebrosidase (also known as acid beta-glucosidase). The enzyme catalyzes the conversion of the glycosphingolipid glucocerebroside (also known as glucosylceramide, a glycolipid) into glucose and ceramide. Deficiency of the enzyme results in the accumulation of glucosylceramide in lysosomes of macrophages giving rise to foam cells (Gaucher cells) in the spleen, liver, kidneys, lungs, brain, bone marrow, and other organs.

Gaucher disease has three common clinical subtypes. Type 1 (non-neuropathic Gaucher disease) is the most common form of the disease. Type 2 (acute infantile neuropathic Gaucher disease) typically begins within 6 months of age. Type 3 (chronic neuropathic Gaucher disease) can begin at any time in childhood or even in adulthood; this type has three subtypes. Treatment may consist of enzyme replacement therapy (ERT) or substrate replacement therapy (SRT).

There are three recombinant glucocerebrosidases used as drugs for ERT: Cerezyme (imiglucerase) Elelyso (taliglucerase alfa) or VPRIV (velaglucerase). All three are based on the human gene sequence for the native enzyme but are differentiated from each other according to the cell type used in production.

Cerezyme (imiglucerase) is an analogue of the human enzyme B-glucocerebrosidase, produced by recombinant DNA technology. Cerezyme is indicated for long-term enzyme replacement therapy for pediatric and adult individuals with a confirmed diagnosis of Type 1 Gaucher disease.

Elelyso (taliglucerase alfa) is a hydrolytic lysosomal glucocerebroside-specific enzyme indicated for the treatment of individuals with a confirmed diagnosis of Type 1 Gaucher disease.

Vpriv (velaglucerase alfa) is a hydrolytic lysosomal glucocerebroside-specific enzyme indicated for long-term enzyme replacement therapy (ERT) for individuals with type 1 Gaucher disease.

Criteria:

Effective 03/01/18: For site of service requirements for Cerezyme and Vpriv, see BCBSAZ Medical Coverage Guideline #O1008, “Site of Service Requirements for Certain Medications”.

See Resources section for FDA-approved dosage.

- Cerezyme (imiglucerase) for the treatment of long-term enzyme replacement therapy in Type 1 Gaucher disease for individuals 2 years of age and older is considered medically necessary with documentation of ANY of the following:
  1. Anemia
  2. Bone disease
  3. Hepatomegaly or splenomegaly
  4. Thrombocytopenia
TREATMENTS FOR GAUCHER DISEASE (cont.)

Criteria: (cont.)

➢ Continuation or renewal of Cerezyme (imiglucerase) therapy for Type 1 Gaucher disease is considered medically necessary with documentation of ALL of the following:

1. TWO of the following:
   - Achieved and maintains a hemoglobin > 11.5 g/dL for females and > 12.5 g/dL for males
   - Achieved and maintains a platelet count > 120,000/mm³
   - Liver volume or size has decreased by at least 25%
   - Spleen volume or size has decrease by at least 25%

2. No evidence of disease progression
3. No evidence the individual developed any contraindications or significant unacceptable adverse drug effects that may exclude continued use

➢ Cerezyme (imiglucerase) for all other indications not previously listed or if above criteria not met is considered experimental or investigational based upon:

1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, but are not limited to:

- Combination SRT and ERT
- Gaucher disease type 2 and type 3
- Treatment with dosing or frequency outside the FDA-approved dosing and frequency
TREATMENTS FOR GAUCHER DISEASE (cont.)

Criteria: (cont.)

- Elelyso (taliglucerase alfa) for individuals 4 years of age and older is considered medically necessary with documentation of a confirmed diagnosis of Type 1 Gaucher disease.

- Continuation or renewal of Elelyso (taliglucerase alpha) therapy for Type 1 Gaucher disease, is considered medically necessary with documentation of ALL of the following:
  1. TWO of the following:
     - Achieved and maintains a hemoglobin > 11.5 g/dL for females and > 12.5 g/dL for males
     - Achieved and maintains a platelet count > 120,000/mm$^3$
     - Liver volume or size has decreased by at least 25%
     - Spleen volume or size has decrease by at least 25%
  2. No evidence of disease progression
  3. No evidence the individual developed any contraindications or significant unacceptable adverse drug effects that may exclude continued use

- Elelyso (taliglucerase alfa) for all other indications not previously listed is considered experimental or investigational based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, but are not limited to:

- Combination SRT and ERT
- Gaucher disease type 2 and type 3
- Treatment with dosing or frequency outside the FDA-approved dosing and frequency
TREATMENTS FOR GAUCHER DISEASE (cont.)

Criteria: (cont.)

- Vpriv (velaglucerase alfa) for individuals 4 years of age and older is considered *medically necessary* for long-term enzyme replacement therapy with documentation of a confirmed diagnosis of Type 1 Gaucher disease.

- Continuation or renewal of Vpriv (velaglucerase alph) therapy for Type 1 Gaucher disease, is considered *medically necessary* with documentation of ALL of the following:
  1. **TWO** of the following:
     - Achieved and maintains a hemoglobin > 11.5 g/dL for females and > 12.5 g/dL for males
     - Achieved and maintains a platelet count > 120,000/mm³
     - Liver volume or size has decreased by at least 25%
     - Spleen volume or size has decrease by at least 25%
   2. No evidence of disease progression
   3. No evidence the individual developed any contraindications or significant unacceptable adverse drug effects that may exclude continued use

- Vpriv (velaglucerase alfa) for all other indications not previously listed is considered *experimental or investigative* based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to*:

- Combination SRT and ERT
- Gaucher disease type 2 and type 3
- Treatment with dosing or frequency outside the FDA-approved dosing and frequency
TREATMENTS FOR GAUCHER DISEASE  (cont.)

Resources:

Literature reviewed 08/27/18. We do not include marketing materials, poster boards and non-published literature in our review.

Cerezyme Package Insert:

- FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term enzyme replacement therapy for pediatric and adult individuals with Type 1 Gaucher disease that results in 1 or more of the following conditions: anemia, bone disease, hepatomegaly or splenomegaly, and thrombocytopenia</td>
<td>For intravenous use only. Infusion over 1-2 hrs. Dosage should be individualized to each individual. Initial dosages range from 2.5U/kg 3 times per week to 60 units/kg once every 2 weeks. 60 U/kg every 2 weeks is the dosage for which the most data are available. Dosage adjustments are made based on assessment and therapeutic goals.</td>
</tr>
</tbody>
</table>

Elyso Package Insert:

- FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>For the treatment of individuals 4 years and older with a confirmed diagnosis of Type 1 Gaucher disease</td>
<td>For long term treatment 60 units/kg of body weight administered every other week as a 1-2 hr. intravenous infusion. For individuals switching from imiglucerase, begin treatment at the same unit/kg dose as the individual’s previous imiglucerase dose. Dosage adjustments can be based on achievement and maintenance of each individual’s therapeutic goals.</td>
</tr>
</tbody>
</table>
TREATMENTS FOR GAUCHER DISEASE (cont.)

Resources: (cont.)

Vpriv Package Insert:

- FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>For the treatment of individuals 4 years and older with a confirmed diagnosis of Type 1 Gaucher disease</td>
<td>For long term treatment 60 units/kg of body weight administered every other week as a 1 hr. intravenous infusion. For individuals switching from imiglucerase, begin treatment at the same unit/kg dose as the individual’s previous imiglucerase dose. Dosage adjustments can be based on achievement and maintenance of each individual’s therapeutic goals.</td>
</tr>
</tbody>
</table>

Initial Approval Duration: 6 months

Renewal Approval Duration: 12 months
TREATMENTS FOR GAUCHER DISEASE (cont.)

Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ’s Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ’s Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Díí kwe’ é atah niilíningíí Blue Cross Blue Shield of Arizona haada yit’éego bíná’ídíjìdo éí doodago Háída bíjá aniyeedígíí t’áadoo le’é yíná’ídíjìdo beehaz’áaníí hólo dóo díí t’áá hazaadk’éhí háká a’doowolgo bee haz’a doo báqáh ilínígóó. Ata’ halné’ígíí kojí’ bích’íí hodiilínih 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話 在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thêm thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thông dịch viên, xin gọi 877-475-4799.

Arabic:
إن كان لديك أو أدى شخص يمساعدة أسلحة بخصوص Blue Cross Blue Shield of Arizona المضروبة بطللكة من دون أية تكلفة للتحدث مع متدرج الصلب ب 877-475-4799.
MEDICAL COVERAGE GUIDELINES
SECTION: DRUGS

TREATMENTS FOR GAUCHER DISEASE (cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutulungan, ay may mga katanungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakau ng tungkol at impormasyon sa iyong wika ng walang gastos. Upang makeusap ang isang tagasalin, tawag sa 877-475-4799.

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona에 대해서 질문이 있다면 귀하는 그러한 도움과 정보를 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 통역사와 매개하기 위해서는 877-475-4799로 전화하십시오.

French: Si vous, ou quelqu'un que vous êtes en train d'aider, a des questions à propos de Blue Cross Blue Shield of Arizona, vous avez le droit d'obtenir de l'aide et l'information dans votre langue à aucun coût. Pour parler à un interprète, appelez 877-475-4799.

German: Falls Sie oder jemand, dem Sie helfen, Fragen zum Blue Cross Blue Shield of Arizona haben, haben Sie das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Um mit einem Dolmetscher zu sprechen, rufen Sie bitte die Nummer 877-475-4799 an.

Russian: Если у вас или лица, которому вы помогаете, имеются вопросы по поводу Blue Cross Blue Shield of Arizona, то вы имеете право на бесплатное получение помощи и информации на вашем языке. Для разговора с переводчиком позвоните по телефону 877-475-4799.

Japanese: ご本人様、またはお客様の身の回りの方でも、Blue Cross Blue Shield of Arizonaについてご質問がございましたら、ご希望の言語でサポートを受けたり、情報を入手したりすることができます。料金はかかりません。通訳とお電話される場合、877-475-4799までお電話ください。

Farsi:

آگز شما، یا کسی که شما به آن کمک می‌کنید، سوال‌های مربوط به آموزش‌های و خدمات بهترین‌هایی که Blue Cross Blue Shield of Arizona در مورد آن‌ها ارائه می‌دهد. 

Assyrian:

Blue Cross Blue Shield of Arizona

Serbo-Croatian: Ukoliko Vi ili neko kome Vi pomažete ima pitanje o Blue Cross Blue Shield of Arizona, imate pravo da besplatno dobijete pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodiocem, nazovite 877-475-4799.

Thai: หากคุณ หรือผู้ที่คุณช่วยเหลือมีคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizona คุณมีสิทธิ์ใช้บริการแปลและข้อมูลภาษาของคุณได้โดยไม่เสียค่าใช้จ่าย ทั้งหมดนี้โปรดติดต่อที่ 877-475-4799