ADAGEN® (pegademase bovine)

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.

**Description:**

Adagen injection is a modified enzyme used for enzyme replacement therapy for the treatment of severe combined immunodeficiency disease (SCID) associated with a deficiency of adenosine deaminase (ADA).

SCID associated with a deficiency of ADA is a rare, inherited, and often fatal disease. In the absence of the ADA enzyme, the purine substrates adenosine and 2-deoxyadenosine accumulate, causing metabolic abnormalities that are directly toxic to lymphocytes.
ADAGEN (pegademase bovine) (cont.)

Criteria:

All requests for Adagen will be reviewed by the medical director(s) and/or clinical advisor(s).

See Resources section for FDA-approved dosage.

- Adagen is considered **medically necessary** for infants from birth or children of any age at the time of diagnosis with documentation of **ALL** of the following:
  1. Severe combined immunodeficiency disease (SCID)
  2. Individual is not a suitable candidate for, or who has failed bone marrow transplantation

- Continuation of Adagen is considered **medically necessary** with documentation of **ALL** of the following:
  1. Achieved and maintains a plasma ADA activity trough level (before maintenance injection) between 15-35 μmol/h/mL
  2. Erythrocyte dATP is reduced to < 0.005-0.015 μmol/mL of packed erythrocytes or is < 1% of the total erythrocyte adenine nucleotide (ATP + dATP) content, with a normal ATP level, as measured in a pre-injection sample
  3. Reduced frequency of infection involving pathogens and opportunistic organisms (e.g., thrush, pneumonia)

- Adagen 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**:

- As a replacement for HLA identical bone marrow transplant therapy
- To replace continued close medical supervision and the initiation of appropriate diagnostic tests and therapy (e.g., antibiotics, nutrition, oxygen, gammaglobulin) as indicated for intercurrent illnesses.
- Treatment with dosing or frequency outside the FDA-approved dosing and frequency
ADAGEN (pegademase bovine) (cont.)

Resources:

Literature reviewed 06/26/18. We do not include marketing materials, poster boards and non-published literature in our review.

Adagen Package Insert:

FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indications</th>
<th>Recommended dose</th>
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<tr>
<td>Enzyme replacement therapy 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. Recommended for use in infants from birth or in children of any age at the time of diagnosis.</td>
<td>Plasma ADA activity and red cell dATP should be determined prior to treatment. Adagen should be administered every 7 days as an intramuscular injection. The dosage should be individualized. The recommended dosing schedule is 10 U/kg for the first dose, 15 U/kg for the second dose and 20 U/kg for the third dose. The usual maintenance dose is 20 U/kg per week. Further increases of 5 U/kg/week may be necessary, but a maximum single dose of 30 U/kg should not be exceeded. Once treatment has been initiated, a desirable range of plasma ADA activity (trough level before maintenance injection) should be 15–35 µmol/hr/mL. Plasma ADA activity (pre-injection) should be determined every 1-2 weeks during the first 8-12 weeks of treatment in order to establish an effective dose. After 2 months of maintenance treatment, red cell dATP levels should decrease to a range of ≤ 0.005 to 0.015 µmol/mL. The normal value of dATP is below 0.001 µmol/mL. Once the level of dATP has fallen adequately, it should be measured 2-4 times a year during the remainder of the first year and 2-3 times a year thereafter, assuming no interruption in therapy. Between 3 and 9 months, plasma ADA should be determined twice a month, then monthly until after 18-24 months of treatment. Individuals who have successfully been maintained on therapy for two years should continue to have plasma ADA measured every 2-4 months and red cell dATP measured twice yearly. More frequent monitoring would be necessary if therapy was interrupted or if an enhanced rate of clearance of plasma ADA activity develops.</td>
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Initial Approval Duration: 6 months

Renewal Approval Duration: 12 months
ADAGEN (pegademase bovine) (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 nilinígíí Blue Cross Blue Shield of Arizona haada yit’éego bina’ídííkidgo éí doodago Háída bijá anilyeeéíííí t’áaddoo le’é yína’ídííkidgo beehaz’ááníí hólo díí t’áá hazaadk’ehíí háká a’doooolgo beez’h’a doo bágí ileégóó. Ata’hálne’íí kojí’ bích’íí hodíííhíin 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 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 لدى شخص تساعدك أسئلة بخصوص Blue Cross Blue Shield of Arizona الضرورية بلغتك من دون أية تكلفة، للتحدث مع مترجم اتصل ب 877-475-4799.
ADAGEN (pegademase bovine) (cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutuuanan, ay maga na katanungan tungkol sa Blue Cross Blue Shield of Arizona, magkarapat ka na makakaha ng tulong at impormasyon sa iyong wika ng walang gastos. Upang makuasa ang isang tagasalin, tumawag sa 877-475-4799.

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona에 관해서 질문이 있다면 귀하는 그러한 도움과 정보를 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 통역사와 얘기하기 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。通訳とお話される場合、877-475-4799までお電話ください。

Farsi: 

آگر شما، یا کسی که شما به او کمک می‌کنید، سوال‌های مربوط به اطلاعاتی که باید از Blue Cross Blue Shield of Arizona دریافت کند، را داشته باشید و حق دارید که کمک و ترجمه بگیرند، شما می‌توانید با 877-475-4799 تماس حاصل نمایید.

Assyrian:

Blue Cross Blue Shield of Arizona

Serbo-Croatian: Ukoiko Vi ili neko kome Vi pomažete ima pitanja 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 หรือคุณช่วยเหลือคนคนอื่นที่มีคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizona คุณมีสิทธิ์ที่จะได้รับความช่วยเหลือและความชัดเจนภาษาของคุณได้โดยไม่มีค่าใช้จ่าย โปรดโทรมา ที่ 877-475-4799