Plasminogen, Human-tvmh (Ryplazim)

Number: 0976

POLICY

Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Note: Requires Precertification.

Precertification of plasminogen, human tvmh (Ryplazim) is required of all Aetna participating providers and members in applicable plan designs. For precertification of Ryplazim, call (866) 752-7021 (commercial), (866) 503-0857 (Medicare), or fax (866) 267-3277.

I. Criteria for Initial Approval

Aetna considers plasminogen, human tvmh (Ryplazim) medically necessary for the treatment of plasminogen deficiency type 1 (hypoplasminogenemia) when *all* of the following criteria are met:

A. Member has a baseline plasminogen activity level of 45% or less at baseline; *and*

B. Member has a documented history of lesions and symptoms consistent with a diagnosis of plasminogen deficiency type 1 (e.g., ligneous conjunctivitis, ligneous gingivitis or gingival overgrowth, vision abnormalities, respiratory distress and/or obstruction, abnormal wound healing).

Aetna considers all other indications as experimental and investigational.

POLICY HISTORY
Effective: 09/10/2021
Next Review: 01/01/2022

Definitions

Additional Information
Clinical Policy Bulletin Notes

II. Continuation of Therapy

Aetna considers continuation of plasminogen, human tvmh (Ryplazim) therapy medically necessary for members with plasminogen deficiency type 1 (hypoplasminogenemia) who are experiencing benefit from therapy as evidenced by disease stability or disease improvement (e.g., improvement in lesion number and/or size, absence of new lesion development, improvement in respiratory function, increased quality of life).

Dosage and Administration

Plasminogen, human-tvmh is available as Ryplazim, which is supplied in a single-dose 50-mL vial containing 68.8 mg of plasminogen as a lyophilized powder for reconstitution with 12.5 mL of Sterile Water for Injection, USP. After reconstitution, each vial will contain 5.5 mg/mL of plasminogen. For intravenous infusion.

The recommended dosage of Ryplazim is 6.6 mg/kg body weight administered intravenously every 2 to 4 days.

Source: Prometic Bioproduction, 2021

BACKGROUND

U.S. Food and Drug Administration (FDA)-Approved Indications

- Ryplazim is plasma-derived human plasminogen indicated for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia).

Plasminogen, human-tvmh, is available as Ryplazim (Prometic Bioproduction, Inc.). Treatment with Ryplazim temporarily increases plasminogen levels in the blood.

Ryplazim is contraindicated in patients with known hypersensitivity to plasminogen, or other components of Ryplazim. The label carries warnings and precautions for the following:

- Bleeding: administration may lead to bleeding at lesion sites or

worsen active bleeding.

- Tissue sloughing: respiratory distress due to tissue sloughing may occur in patients with mucosal lesions in the tracheobronchial tree following Ryplazim administration.
- Transmission of infectious agents: Ryplazim is made from human blood and therefore carries a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob Disease (CJD) agent.
- Hypersensitivity reactions, including anaphylaxis, may occur.
- Neutralizing antibodies (inhibitors) may develop, although were not observed in clinical trials. If clinical efficacy is not maintained (e.g., development of new or recurrent lesions),then determine plasminogen activity levels in plasma.
- Laboratory abnormalities: Patients receiving Ryplazim may have elevated blood levels of D-dimer. D-dimer levels will lack interpretability in patients being screened for venous thromboembolism (VTE).

The most frequent (incidence 10% or more) adverse reactions in clinical trials were abdominal pain, bloating, nausea, fatigue, extremity pain, hemorrhage, constipation, dry mouth, headache, dizziness, arthralgia, and back pain.

Plasminogen Deficiency Type 1

Plasminogen deficiency type 1, also referred to as hypoplasminogenemia, is a rare genetic disorder characterized by decreased plasminogen levels that causes formation of fibrin-rich, ligneous ("wood-like") pseudomembranous lesions on mucous membranes that can impair normal tissue and organ function. Overall severity of the disorder can vary greatly from one person to another depending where the lesions, or growths, occur. The most common symptom is ligneous conjunctivitis, which can lead to blindness. However, the condition can affect other areas of the body which can lead to serious complications (e.g., obstruction of the airways). Plasminogen deficiency type 1 is caused by mutations in the *PLG* gene, which is inherited in an autosomal recessive pattern. *PLG* mutations can decrease the amount of plasminogen that is produced, alter its function, or both. When the mutations affect plasminogen levels as well as the activity of the protein, plasminogen deficiency type 1 results. There is currently no screening test available; molecular genetic testing can only confirm a diagnosis. Diagnosis

therefore generally relies on clinical symptoms, family medical history, and confirmatory testing. The growths usually recur if they are removed. Replacement therapy increases the plasma level of plasminogen enabling a temporary correction of the plasminogen deficiency and reduction or resolution of extravascular fibrinous lesions (NIH, 2016; NORD, 2016; Prometic Bioproduction, 2021).

On June 4, 2021, the U.S. Food and Drug Administration (FDA) approved Ryplazim (plasminogen, human-tvmh) for the treatment of patients with plasminogen deficiency type 1. FDA approval was based on one single-arm, open-label (unblinded) clinical trial that evaluated the efficacy and safety of Ryplazim in patients with plasminogen deficiency type 1. The clinical trial included a total of 15 patients who had a baseline plasminogen activity level between less than 5% and 45% of normal, and biallelic mutations in the plasminogen (*PLG*) gene. The age range was 4 to 42 years old, including 6 pediatric patients age 4 to 16 years, and 9 adults. All patients received Ryplazim at a dose of 6.6 mg/kg administered every 2 to 4 days for 48 weeks to achieve at least an increase of individual trough plasminogen activity by an absolute 10% above baseline and to treat the clinical manifestations of the disease. Efficacy was established on the basis of overall rate of clinical success at 48 weeks. Overall rate of clinical success is defined as 50% of patients with visible or other measurable non-visible lesions achieving at least 50% improvement in lesion number/size, or functionality impact from baseline. Spirometry was the only test of organ function used and one patient had abnormal spirometry at baseline. This patient had a history of ligneous airway disease with a severe obstructiveventilatory defect (FEV1: 46.7% of predicted normal) at baseline prior to treatment that corrected to normal (FEV1: 89.3% of predicted normal) after 12 weeks of treatment. All patients with any lesion at baseline had at least 50% improvement in the number/size of their lesions (FDA, 2021; Prometic Bioproduction, 2021).

The outcome from the trial on patients with external lesions found that 25 of the 32 (78%) external lesions [with sites mainly located in the eyes (ligneous conjunctivitis), nose, gums (ligneous gingivitis), ligneous lesions of the hands and feet] were resolved by the end of Week 48. There were no recurrent or new external lesions in any patient through Week 48. The outcome from the trial on patients with internal lesions found that 9 of the 12 (75%) assessed internal lesions were resolved by Week 48. The lesion sites were mainly located in the cervix, bronchus, colon, vagina

and uterus. No recurrent or new lesions were found on imaging in any patient through Week 48 (Prometic Bioproduction, 2021).

In summary, the effectiveness of Ryplazim was demonstrated by at least 50% improvement of the patient's lesions in all 11 patients who had lesions at baseline, and absence of recurrent or new lesions in any of the 15 patients through the 48 weeks of treatment.

CPT Codes/ HCPCS Codes/ICD-10 Codes
Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+"

Code	Code Description
Other CPT codes related to the CPB:	
96365 – 96368	Intravenous infusion administration
HCPCS codes covered if selection criteria are met:	
Human-tvmh (Ryplazim) - No specific code	
ICD-10 codes covered if selection criteria are met:	
E88.02	Plasminogen deficiency

The above policy is based on the following references:

1. Celkan T. Plasminogen deficiency. J Thromb Thrombolysis. January, 2017; 43(1):132-138.
2. National Institutes of Health (NIH). Type 1 plasminogen deficiency. Genetic and Rare Diseases Information Center (GARD). Bethesda, MD: NIH; updated June 2016.
3. National Organization for Rare Disorders (NORD). Congenital plasminogen deficiency. NORD Rare Disease Database. Danbury, CT: NORD; updated May 2016.
4. Prometic Bioproduction, Inc. Ryplazim - plasminogen injection, powder, lyophilized, for solution. Laval, Quebec, Canada: Prometic Bioproduction; revised June 2021.
5. Shapiro AD, Nakar C, Parker JM, et al. Plasminogen replacement therapy for the treatment of children and adults with congenital plasminogen deficiency. Blood. 2018;131(12):1301-1310.
6. U.S. Food and Drug Administration (FDA). FDA approves first treatment for patients with plasminogen deficiency, a rare genetic disorder. Press Release. Silver Spring, MD: FDA; June 4, 2021.

AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to Aetna Clinical Policy Bulletin Number: 0976 Plasminogen, Human-tvmh (Ryplazim)

There are no amendments for Medicaid.

new 09/10/2021

PROVIDER BULLETIN
PROVIDER INFORMATION

BlueCross BlueShield Minnesota

February 1, 2021

New Medical, Medical Drug and Behavioral Health Policy Management Updates—Effective April 5, 2021

Blue Cross and Blue Shield of Minnesota and Blue Plus (Blue Cross) will be expanding utilization management requirements, including prior authorization (PA) requirements.

As stewards of healthcare expenditures for our subscribers, we are charged with ensuring they receive the highest quality, evidence-based care. This is accomplished through expanded development of medical policies and through management of these policies to include the PA process. The primary purpose of the PA process is to ensure that evidence-based care is provided to our subscribers, driving quality, safety, and affordability.

The following prior authorization changes will be effective April 5, 2021:

Policy #	Policy Title/ Service	New Policy	Prior Authorization Requirement	Line(s) of Business
II-173	Accepted Indications for Medical Drugs Which Are Not Addressed by a Specific Medical Policy • Plasminogen (Ryplazim™)*	No	New	Commercial
L33394	Coverage for Drugs & Biologics for Label & Off-Label Uses: • Plasminogen (Ryplazim™)*	No	New	Medicare Advantage

* PA will be required upon FDA approval.

Products Impacted

The information in this bulletin applies **only** to subscribers who have coverage through Commercial and Medicare Advantage lines of business.

Submitting a PA Request when Applicable

- **Providers may submit PA requests for any treatment in the above table starting March 29, 2021.**
- Providers must check applicable Blue Cross policy and **attach all required clinical documentation** with the PA request. PA requests will be reviewed when patient-specific, relevant medical documentation has been submitted supporting the medical necessity of the service**.** Failure to submit required information may result in review delays or a denial of the request due to insufficient information to support medical necessity. If a provider does not obtain the required PA before rendering services, Blue Cross will deny claims as provider liability for lack of prior authorization.
- PA approval will be based on the Blue Cross policy criteria. To review Blue Cross criteria:

    - Go to providers.bluecrossmn.com
    - Under Tools & Resources, select "Medical Policy", and read/accept the Blue Cross Medical Policy Statement
    - Select the "+" (plus) sign next to Medical and Behavioral Health Policies, then select "Blue Cross Blue Shield of Minnesota Medical Policies" to access policy criteria.
- Current and future PA requirements can be found using the *Is Authorization Required* tool in the Availity® portal prior to submitting a PA request. Prior Authorization Lists are also updated to reflect additional PA requirements on the effective date of the management change and includes applicable codes. To access the pdf Prior Authorization Lists for all lines of business:
    - Go to providers.bluecrossmn.com
    - Under Tools & Resources, select "Medical Policy", and read/accept the Blue Cross Medical Policy Statement
    - Select the "+" (plus) sign next to "Utilization Management" to access the Prior Authorization Lists.
- If a provider does not obtain the required PA before rendering services, Blue Cross will deny claims as provider liability for lack of prior authorization. The requirement applies to subscribers starting therapy and to those already being treated with a therapy noted above.

Prior Authorization Requests

- Participating providers must submit PA requests online via our free Availity® provider portal.
- For medical drugs, PA's can also be submitted using a NCPDP standard XML file feed to Blue Cross through CenterX, via an integrated Electronic Medical Record (EMR) system. To learn how to do this, providers should contact their EMR vendor for assistance.
- Out of state, non-contracted providers can submit a PA request to Blue Cross by either using the electronic processes above, the fax form located under the Forms & Publications section on the Blue Cross website, or their own PA form.

Note: An approved PA does not guarantee coverage under a subscriber's benefit plan. Subscriber benefit plans vary in coverage and some plans may not provide coverage for certain services discussed in the medical policies.

Reminder Regarding Medical Policy Updates & Changes:

Medical Policy changes are communicated in the Upcoming Medical Policy Notifications section of the Blue Cross Medical and Behavioral Health Policy website. The Upcoming Policies section lists new, revised, or inactivated policies approved by the Blue Cross Medical and Behavioral Health Policy Committee and are effective at minimum 45 days from the date they were posted. To access the website:

- Go to providers.bluecrossmn.com
- Under Tools & Resources, select "Medical Policy", and read/accept the Blue Cross Medical Policy Statement
- Select the "+" (plus) sign next to "Medical and Behavioral Health Policies" to see the Upcoming Medical Policy Notifications section

Questions?

If you have questions, please contact provider services at (**651**) **662-5200** or **1-800-262-0820**.

Corporate Medical Policy: Plasminogen, human-tvmh (Ryplazim®)

Restricted Product(s):

- plasminogen, human-tvmh (Ryplazim®) intravenous infusion for administration by a healthcare professional

FDA Approved Use:

- For treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia)

Criteria for Medical Necessity:

The restricted product(s) may be considered medically necessary when the following criteria are met:

Initial Criteria for Approval:

1. The patient is 11 months of age or older; **AND**
2. The patient has a diagnosis of plasminogen deficiency type 1 (hypoplasminogenemia) **[medical record documentation required]**; **AND**
3. The patient has a baseline plasminogen activity level ≤ 45% prior to treatment **[medical record documentation required]**; **AND**
4. The patient has a history of lesions and symptoms consistent with a diagnosis of congenital plasminogen deficiency **[medical record documentation required]**; **AND**
5. The prescriber is a specialist in the area of the patient's diagnosis or has consulted with a specialist in the area of the patient's diagnosis **[medical record documentation required]**; **AND**
6. The requested quantity does NOT exceed the maximum units allowed for the duration of approval (see table below); **AND**
7. For requests for injection or infusion administration of the requested medication in an **inpatient or outpatient hospital setting**, Site of Care Criteria applies (outlined below)*

   Duration of Approval: 90 days (12 weeks)

Continuation Criteria for Approval:

1. The patient was approved through Blue Cross NC initial criteria for approval; **OR**
2. The patient would have met initial criteria for approval at the time they started therapy **[medical record documentation required]**; **AND**
3. The patient has had a clinically significant response to treatment with the requested agent, as defined by one of the following **[medical record documentation required]**:
   a. The patient has resolution or improvement of baseline lesions (if present) with no new or recurrent lesions; **OR**

   b. The patient has achieved or maintained a trough plasminogen activity level ≥ 10% above the initial baseline level; **AND**
4. The prescriber is a specialist in the area of the patient's diagnosis or has consulted with a specialist in the area of the patient's diagnosis **[medical record documentation required]**; **AND**
5. The requested quantity does NOT exceed the maximum units allowed for the duration of approval (see table below); **AND**
6. For requests for injection or infusion administration of the requested medication in an **inpatient or outpatient hospital setting**, Site of Care Criteria applies (outlined below)*

Duration of Approval: 365 days (1 year)

FDA Label Reference				
Medication	**Indication**	**Dosing**	**HCPCS**	**Maximum Units***
plasminogen, human-tvmh (Ryplazim®) intravenous (IV) infusion	Plasminogen deficiency type 1 (hypoplasminogenemia) in patients ≥11 months old	IV: 6.6 mg/kg administered every 2 to 4 days (total infusion volume based on final plasminogen concentration of 5.5 mg/mL); see package insert for full dosing details	C9399** J3490** J3590**	Initial: **30,360** Continuation: **120,780**

***Maximum units allowed for duration of approval**
****Non-specific assigned HCPCS codes, must submit requested product NDC**

***Site of Care Medical Necessity Criteria**

1. For requests for injection or infusion administration in an **inpatient setting**, the injection or infusion may be given if the above medical necessity criteria are met AND the inpatient admission is NOT for the sole purpose of administering the injection or infusion; **OR**
2. For requests for injection or infusion administration in an **outpatient hospital setting**, the injection or infusion may be given if the above medical necessity criteria are met AND ONE of the following must be met:
   a. History of mild adverse events that have not been successfully managed through mild pre-medication (e.g., diphenhydramine, acetaminophen, steroids, fluids, etc.); **OR**
   b. Inability to physically and cognitively adhere to the treatment schedule and regimen complexity; **OR**
   c. New to therapy, defined as initial injection or infusion OR less than 3 months since initial injection or infusion; **OR**
   d. Re-initiation of therapy, defined as ONE of the following:

   i. First injection or infusion after 6 months of no injections or infusions for drugs with an approved dosing interval less than 6 months duration; **OR**
   ii. First injection or infusion after at least a 1-month gap in therapy outside of the approved dosing interval for drugs requiring every 6 months dosing duration; **OR**
e. Requirement of a change in the requested restricted product formulation; **AND**

3. If the Site of Care Medical Necessity Criteria in #1 or #2 above are not met, the injection or infusion will be administered in a **home-based infusion** or physician office setting with or without supervision by a certified healthcare professional.

References: all information referenced is from FDA package insert unless otherwise noted below.

1. Shapiro AD, Nakar C, Parker JM, et al. Plasminogen replacement therapy for the treatment of children and adults with congenital plasminogen deficiency. *Blood*. 2018 Mar;131(12):1301-1310.

Policy Implementation/Update Information

September 2021: Original medical policy criteria issued.

Non-Discrimination and Accessibility Notice

Discrimination is Against the Law

- Blue Cross and Blue Shield of North Carolina ("Blue Cross NC") complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex.
- Blue Cross NC does not exclude people or treat them differently because of race, color, national origin, age, disability, or sex.

Blue Cross NC:

- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters

- Information written in other languages

- If you need these services, contact Customer Service **1-888-206-4697**, TTY and TDD, call **1-800-442-7028**.

- If you believe that Blue Cross NC 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:
  - Blue Cross NC, PO Box 2291, Durham, NC 27702, Attention: Civil Rights Coordinator- Privacy, Ethics & Corporate Policy Office, Telephone **919-765-1663**, Fax **919-287-5613**, TTY **1-888-291-1783** civilrightscoordinator@bcbsnc.com

- You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, Civil Rights Coordinator - Privacy, Ethics & Corporate Policy Office 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, D.C. 20201 **1-800-368-1019, 800-537-7697** (TDD). Complaint forms are available at *http://www.hhs.gov/ocr/office/file/index.html*.

- This Notice and/or attachments may have important information about your application or coverage through Blue Cross NC. Look for key dates. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call Customer Service **1-888-206-4697**.

ATTENTION: If you speak another language, language assistance services, free of charge, are available to you. Call 1-888-206-4697 (TTY: 1-800-442-7028).

ATENCIÓN: Si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 1-888-206-4697 (TTY: 1-800-442-7028).

注意：如果您講廣東話或普通話， 您可以免費獲得語言援助服務。請致電 1-888-206-4697
(TTY：1-800-442-7028）。

CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 1-888-206-4697 (TTY: 1-800-442-7028).

주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다. 1-888-206-4697 (TTY: 1- 800-442-7028)번으로 전화해 주십시오.

ATTENTION : Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 1-888-206-4697 (ATS : 1-800-442-7028).

ملحوظة: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية تتوافر لك بالمجان. اتصل برقم 1-888-206-4697. المبرقة الكاتبة: 1-800-442-7028.

LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1-888-206-4697 (TTY: 1-800-442-7028).

ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода. Звоните 1-888-206-4697 (телетайп: 1-800-442-7028).

PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nang walang bayad. Tumawag sa 1-888-206-4697 (TTY: 1-800-442-7028).

સુચના: જો તમે ગુજરાતી બોલતા હો, તો નિ:સુલ્કુ ભાષા સહાય સેવાઓ તમારા માટે ઉપલબ્ધ છે. ફોન કરો 1-888-206-4697 (TTY: 1-800-442-7028).

ចំណាំ៖ ប្រសិនបើលោកអ្នកនិយាយជាភាសាខ្មែរ សេវាកម្មជំនួយផ្នែកភាសាមានផ្តល់ជូនសម្រាប់លោកអ្នកដោយមិនគិតថ្លៃ។ សូមទំនាក់ទំនងតាមរយៈលេខ៖ 1-888-206-4697 (TTY: 1-800-442-7028)។

ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zur Verfügung. Rufnummer: 1-888-206-4697 (TTY: 1-800-442-7028).

ध्यान दें: यदि आप हिन्दी बोलते हैं तो आपके लिए मुफ्त में भाषा सहायता सेवाएं उपलब्ध हैं। 1-888-206-4697 (TTY: 1-800-442-7028) पर कॉल करें।

ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ, ໂດຍບໍ່ເສັງຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 1-888-206-4697 (TTY: 1-800-442-7028).

注意事項：日本語を話される場合、無料の言語支援をご利用いただけます。1-888-206-4697（TTY: 1-800-442-7028）まで、お電話にてご連絡ください。

Show

BlueCross BlueShield of Tennessee Medical Policy Manual

Plasminogen, human-tvmh (Ryplazim®)

NDC CODE(S) 70573-0099-XX RYPLAZIM 5.5MG/ML (Prometic Bioproduction, Inc)

DESCRIPTION

Plasminogen, human-tvmh is a Glu-plasminogen which is the native circulating form of plasminogen in the blood. Treatment with plasminogen, human-tvmh temporarily increases plasminogen levels in blood.

POLICY

- Plasminogen, human-tvmh for the treatment of plasminogen deficiency type 1 (hypoplasminogenemia) is considered ***medically necessary*** if the medical appropriateness criteria are met. **(See Medical Appropriateness below.)**
- Plasminogen, human-tvmh for the treatment of other conditions/diseases is considered ***investigational.***

MEDICAL APPROPRIATENESS

INITIAL APPROVAL CRITERIA

- Patient is at least 11 months of age; **AND**
- Patient blood pressure is controlled prior to initiation of treatment; **AND**
- Patient has healing of lesions or wounds suspected as a source of a recent bleeding event prior to initiating therapy; **AND**
- Patient has had a baseline plasminogen activity measured prior to therapy and plasminogen activity level is ≤ 45% (Note: If patient is receiving plasminogen supplementation with fresh frozen plasma, allow for a 7-day washout period before obtaining baseline plasminogen activity level); **AND**

Universal Criteria

- Patients on concomitant therapy with anticoagulants, antiplatelet drugs, or other agents which may interfere with normal coagulation will be monitored during and for 4 hours after infusion of Ryplazim®; **AND**

Plasminogen Deficiency Type 1 (Hypoplasminogenemia)

- Patient has a history of visible or non-visible lesions (e.g., confirmed by computed tomography, magnetic resonance imaging, ultrasound, etc.)

Note: All patients must initiate therapy at a frequency of every three days.

RENEWAL CRITERIA

- Patient continues to meet indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in initial approval criteria; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe bleeding, respiratory distress, anaphylaxis and severe allergic reactions, etc.; **AND**
  - Patient has demonstrated a beneficial response to therapy (i.e., resolution of lesions); **OR**
  - Patient's lesions have not resolved after an initial 12 weeks of therapy OR there are new or recurrent lesions; **AND**
    - Patient may increase dosage frequency, as outlined below, in one day increments every 4-8 weeks up to the max dosing frequency (i.e., every two days); **AND**
    - Re-assess trough plasminogen activity level if, after 12 additional weeks of dose optimization, no clinical effect has been noted; **AND**
      - If trough plasminogen activity level is <10% above baseline, repeat trough. If low plasminogen is confirmed AND no clinical effect has been demonstrated, consider treatment discontinuation

DOSAGE/ADMINISTRATION

INDICATION	DOSE
Type 1 Hypo-plasminogenemia	The recommended dosage of Ryplazim is 6.6 mg/kg of body weight administered intravenously every 2 to 4 days. Initiate dosing at a frequency of every three days, then adjust as below. Determination of Dosing Frequency • Obtain baseline plasminogen activity level (allow for a 7-day washout period if the patient has been receiving fresh frozen plasma); **AND** • Obtain trough plasminogen activity level 72 hours following the initial dose and prior to the second dose; **AND** – Plasminogen activity level is <10% above baseline, increase frequency of therapy to every 2 days – Plasminogen activity level is ≥10 and ≤20% above baseline, maintain therapy at frequency of every 3 days – Plasminogen activity level is >20% above baseline, decrease frequency of therapy to every 4 days • Maintain dosing frequency above for 12 weeks while treating active lesions; **AND** – If lesions have resolved, continue therapy and re-assess in 12 weeks – If lesions have not resolved, or there are new or recurrent lesions, increase the dosing frequency in one-day increments every 4-8 week up to dosing every 2 days. If desired clinical effect is not seen in 12 weeks, assess trough plasminogen activity level; **AND** o Plasminogen activity level ≥10% above baseline, consider other additional treatments (e.g., surgical removal) o Plasminogen activity level <10% above baseline, then repeat trough to confirm. If low trough is confirmed, consider discontinuing therapy if no clinical efficacy has been demonstrated
Plasminogen activity (%) as absolute change	

LENGTH OF AUTHORIZATION

Coverage will be provided initially for 12 weeks.

- In patients with complete response, coverage will be renewed annually thereafter.
- In patients with less than complete response, coverage will be renewed for an additional 12 weeks to optimize frequency of administration.

DOSING LIMITS

Max Units (per dose and over time) [HCPCS Unit]:

- 757 mg (11 vials) every 2 days

APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the Medical Policy and a health plan, the express terms of the health plan will govern.

ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

SOURCES

1. Ryplazim [package insert]. Laval, Quebec, CA; Prometric Bioproduction, Inc.; June 2021. Accessed June 2021.

2. Shapiro AD, Nakar C, Parker JM,. Plasminogen replacement therapy for the treatment of children and adults with congenital plasminogen deficiency. Blood. 2018 Mar 22;131(12):1301-1310. doi: 10.1182/blood-2017-09-806729. Epub 2018 Jan 10..

3. MICROMEDEX Healthcare Series. Drugdex Drug Evaluations. (2021, June). Plasminogen, human-tvmh. Retrieved July 19, 2021 from MICROMEDEX Healthcare Series.

ORIGINAL EFFECTIVE DATE: 9/30/2021

MOST RECENT REVIEW DATE: 9/30/2021

ID_MRx

Clinical Policy: Plasminogen, human-tvmh (Ryplazim)

Reference Number: CP.PHAR.513
Effective Date: 06.04.21
Last Review Date: 11.21
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Plasminogen (Ryplazim®) is a plasma-derived human plasminogen.

FDA Approved Indication(s)

Ryplazim is indicated for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia).

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Ryplazim is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Plasminogen Deficiency Type 1 (must meet all)**:**

1. Diagnosis of symptomatic congenital plasminogen deficiency (C-PLGD) as evidenced by documentation of all of the following (a, b, and c):
   a. Presence of a *PLG* mutation;
   b. Plasminogen activity level ≤ 45%;
   c. Signs or symptoms consistent with C-PLGD (*see Appendix D*);
2. Prescribed by or in consultation with a hematologist;
3. Age ≥ 2 years;
4. Dose does not exceed 6.6 mg/kg every second, third, or fourth day (*based upon individual pharmacokinetics*).

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Plasminogen Deficiency Type 1 (must meet all)**:**

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;

2. If member has received at least 3 months of Ryplazim treatment, increased trough plasminogen activity by at least 10% from baseline;
3. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in C-PLGD-associated signs or symptoms (e.g., improvement in the size of visible lesions, imaging of nonvisible lesions, or spirometry if pulmonary involvement (*see Appendix D*));
4. If request is for a dose increase, new dose does not exceed 6.6 mg/kg every second, third, or fourth day (*based upon individual pharmacokinetics*).

Approval duration: 12 months

B. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
C-PLGD: congenital plasminogen deficiency
FDA: Food and Drug Administration

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): known hypersensitivity to plasminogen, or other components of Ryplazim
- Boxed warning(s): none reported

Appendix D: Clinical Signs and Symptoms of Congenital Plasminogen Deficiency
C-PLGD (also known as type 1 plasminogen deficiency or hypoplasminoginemia) is a rare autosomal-recessive disorder of the fibrinolytic system. The primary manifestation is development of abnormal extravascular accumulation or growth of fibrin-rich, woody (ligneous) pseudomembranous lesions on mucous membranes throughout the body. Wound healing also may be impaired. The disease appears to be most severe in infants and children. Examples of lesion locations and associated complications (not all inclusive):

- Conjunctival lesions “ligneous conjunctivitis” - most common lesion (may result in visual impairment or blindness)
- Tracheobronchial or renal lesions (may result in respiratory or renal failure)

- Lesions in the cerebral ventricular system (may result in congenital occlusive hydrocephalus)
- Lesions in the ears, nasopharynx, and oral cavity (may result in hearing loss, ligneous tonsillitis or ligneous gingivitis with tooth loss)
- Lesions in the genitourinary tract (may result in dysmenorrhea, abnormal menses, dyspareunia or infertility)

_____

Shapiro, Amy D. et al. An international registry of patients with plasminogen deficiency (HISTORY). Haematologica. 2020 Mar; 105(3):554-561.

Appendix E: Ryplazim Pivotal Trial

- In a pivotal phase 2/3 clinical trial for the treatment of C-PLGD, 15 patients with C-PLGD were enrolled, including six pediatric patients, for 48 weeks of therapy with Ryplazim.
- All patients treated with Ryplazim achieved the targeted increase from baseline in their individual trough plasminogen activity levels through 12 weeks of therapy.
- In addition, all patients who had active visible lesions when enrolled in the trial had complete healing of their measurable lesions within 48 weeks of initiating therapy.
- Adverse events reported in the clinical study were characterized as mild, with no patient deaths, serious adverse events or adverse events that caused study discontinuation.

_____

1. *Shapiro, Amy D. et al. Plasminogen replacement therapy for the treatment of children and adults with congenital plasminogen deficiency. Blood. 2018 Mar 22; 131(12):1301-1310.*
2. *A study of Prometic plasminogen IV infusion in subjects with hypoplasminogenemia. Trial record 2 of 2 for: 2002C011G. ClinicalTrials.gov Identifier: NCT02690714. Available at: https://clinicaltrials.gov/ct2/show/NCT02690714?term=2002C011G&draw=2&rank=2. Accessed October 1, 2020.*

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
C-PLGD	6.6 mg/kg body weight given every 2 to 4 days (*based upon individual pharmacokinetics*)	6.6 mg/kg

VI. Product Availability

Single-dose vial: 68.8 mg in 50 ml vial (5.5 mg/ml of plasminogen after reconstitution)

VII. References

1. Ryplazim Prescribing Information. Prometic Bioproductions Inc: Laval, Quebec, Canada; June 2021. Available at: https://www.fda.gov/media/149806/download. Accessed July 6, 2021.
2. Product Pipeline: Plasminogen Deficiency. Liminal BioSciences, Inc. Available at: https://liminalbiosciences.com/pipeline/plasminogen/plasminogen-deficiency-clinical-trials/. Accessed October 1, 2020.
3. Shapiro, Amy D. et al. An international registry of patients with plasminogen deficiency (HISTORY). Haematologica. 2020 Mar; 105(3):554-561.
4. Shapiro, Amy D. et al. Plasminogen replacement therapy for the treatment of children and adults with congenital plasminogen deficiency. Blood. 2018 Mar 22; 131(12):1301-1310.

5. Mehta R, Shapiro AD. Plasminogen deficiency. Haemophilia. 2008; 14, 1261–1268. DOI: 10.1111/j.1365-2516.2008.01825.x.
6. Schuster V, Hugle B, Tefs K. Plasminogen deficiency. J Thromb Haemost 2007; 5:2315–22.
7. Tefs K, Gueorguieva M, Klammt J, et al. Molecular and clinical spectrum of type I plasminogen deficiency: a series of 50 patients. Blood, 1 November 2006; 108(9):3021-3026.
8. A treatment protocol for expanded access administration of Prometic plasminogen due to closure of clinical trial. Trial record 1 of 2 for: 2002C011G. ClinicalTrials.gov Identifier: NCT03642691. Available at: https://clinicaltrials.gov/ct2/show/NCT03642691?term=2002C011G&draw=2&rank=1. Accessed October 1, 2020.
9. A study of Prometic plasminogen IV infusion in subjects with hypoplasminogenemia. Trial record 2 of 2 for: 2002C011G. ClinicalTrials.gov Identifier: NCT02690714. Available at: https://clinicaltrials.gov/ct2/show/NCT02690714?term=2002C011G&draw=2&rank=2. Accessed October 1, 2020.
10. Type 1 plasminogen deficiency. Genetic and Rare Diseases Information Center. National Institutes of Health. Available at https://rarediseases.info.nih.gov/diseases/4380/type-1-plasminogen-deficiency. Accessed October 6, 2020.

Coding Implications [Pending]
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
Pending	Pending

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively	10.01.20	11.20
4Q 2021 annual review: RT4: drug is now FDA-approved; criteria updated per FDA labeling; modified continuation of therapy to require increased trough plasminogen activity; modified examples of positive response to remove qualification of one year on treatment; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	07.06.21	11.21

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in

developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Effective Date **3/1/2022**
Next Review Date… **3/1/2023**
Coverage Policy Number **IP0382**

Plasminogen

Table of Contents

Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for **Ryplazim®** (plasminogen) human-tvmh intravenous infusion.

Medical Necessity Criteria

Plasminogen (Ryplazim) is considered medically necessary when the following are met:

1. **Plasminogen Deficiency Type 1 (Hypoplasminogenemia).** Individual meets **ALL** of the following criteria (A, B, and C):
    A. Documented diagnosis of plasminogen deficiency type 1 confirmed by **BOTH** of the following:
        i. Biallelic mutations in the *PLG* gene
        ii. Baseline plasminogen activity level ≤ 45% of normal based on the reference range for the reporting laboratory
    B. Individual has a history of lesions and symptoms consistent with a diagnosis of congenital plasminogen deficiency

C. The medication is prescribed by, or in consultation with, a hematologist

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

Reauthorization Criteria

Plasminogen (Ryplazim) is considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration: up to 3 months.

Reauthorization approval duration: up to 12 months.

Conditions Not Covered

Plasminogen (Ryplazim) is considered experimental, investigational or unproven for **ANY** other use.

Coding / Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J3490	Unclassified drugs

Background

OVERVIEW
Ryplazim, a plasma-derived human plasminogen, is indicated for the treatment of patients with **plasminogen deficiency type 1 (hypoplasminogenemia)**.[1]

Disease Overview
Congenital plasminogen deficiency is an ultra-rare, autosomal recessive disease affecting approximately 500 patients in the US (estimated prevalence of 1.6 per million individuals).[2] Female predominance has been reported. The median age of first clinical manifestations has been reported as approximately 10 months in one case series.[3] Type 1 deficiency is considered "true" plasminogen deficiency and results in decreased plasminogen antigen and activity levels.[3] Type 2 deficiency is referred to as dysplasminogenemia; plasminogen antigen levels are normal, but functional activity is reduced. Type 2 deficiency is asymptomatic and not clinically relevant. By contrast, type 1 deficiency may present with multisystem disease characterized by fibrin-rich ("woody") pseudomembranes on mucous membranes.[2] Treatment of congenital plasminogen deficiency should be coordinated by a hematologist who is knowledgeable about the disorder.[4]

Clinical Efficacy

Clinical efficacy of Ryplazim was evaluated in one Phase II/III pivotal study in patients with plasminogen deficiency type 1 (n = 15). All patients had a baseline plasminogen activity level between < 5% and 45% of normal, as well as biallelic mutations in the *PLG* (plasminogen) gene.[1] The primary clinical efficacy endpoint was overall clinical success. Overall clinical success was defined as 50% of patients with visible or other measurable lesions achieving at least a 50% improvement in lesion number/size or functionality impact from baseline. Patients were not required to have active lesions at baseline; however, they were required to have a history of lesions and symptoms consistent with a diagnosis of congenital plasminogen deficiency. Among the 15 patients in the study, a total of 32 external lesions and 12 internal lesions were evaluated. The majority of lesions were resolved by Week 48; no patients experienced new or recurrent lesions.

Dosing Information

Ryplazim dosing frequency is adjusted based on trough plasminogen activity level; the most frequent recommended dosing interval is once every other day. It is recommended to continue dosing for 12 weeks while treating active lesions and then assess for clinical response. If lesions do not resolve by 12 weeks, or if there are new or recurrent lesions, dosing frequency can be escalated (to a maximum of every other day) while assessing clinical improvement until lesion resolution or until the lesions stabilize without further worsening. If desired clinical change does not occur by 12 weeks, an additional trough plasminogen activity level should be obtained. If the trough level is ≥ 10% (absolute change in plasminogen activity) above baseline, surgical removal of the lesions should be considered in addition to plasminogen treatment. If the trough level is < 10% baseline (in combination with no clinical efficacy), consider discontinuing plasminogen treatment due to the possibility of neutralizing antibodies.

References

1. Ryplazim® intravenous infusion [prescribing information]. Laval, Quebec, Canada: Prometic; June 2021.
2. Shapiro AD, Menegatti M, Palla R, et al. An international registry of patients with plasminogen deficiency (HISTORY). *Haematologica*. 2020 Mar; 105(3):554-561.
3. Schuster V, Hügle B, Tefs K. Plasminogen deficiency. *J Thromb Haemost*. 2007 Dec; 5(12):2315-22.
4. Congenital Plasminogen Deficiency. National Organization for Rare Disorders. Updated 2021. Available at: https://rarediseases.org/rare-diseases/congenital-plasminogen-deficiency/. Accessed on December 27, 2021.

Empire BlueCross BlueShield
An Anthem Company

Provider Bulletin
October 2021

Medical drug benefit *Clinical Criteria* updates

On August 20, 2021, the Pharmacy and Therapeutics (P&T) Committee approved the following *Clinical Criteria* applicable to the **medical drug benefit** for Empire BlueCross BlueShield HealthPlus. These policies were developed, revised, or reviewed to support clinical coding edits.

Visit ***Clinical Criteria*** to search for specific policies. If you have questions or would like additional information, use this **email**.

Please see the explanation/definition for each category of *Clinical Criteria* below:

- New: newly published criteria
- Revised: addition or removal of medical necessity requirements, new document number
- Updates marked with an asterisk (*) notate that the criteria may be perceived as more restrictive

Please share this notice with other members of your practice and office staff.

Note: The *Clinical Criteria* listed below applies only to the medical drug benefits contained within the member's medical policy. This does not apply to pharmacy services.

Effective date	Document number	*Clinical Criteria* title	New or revised
November 29, 2021	ING-CC-0202*	Saphnelo (anifrolumab-fnia)	New
November 29, 2021	ING-CC-0203*	Ryplazim (plasminogen, human-tvmh)	New
November 29, 2021	ING-CC-0010*	Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors	Revised
November 29, 2021	ING-CC-0034*	Hereditary Angioedema Agents	Revised
November 29, 2021	ING-CC-0027*	Denosumab Agents	Revised
November 29, 2021	ING-CC-0001*	Erythropoiesis Stimulating Agents	Revised
November 29, 2021	ING-CC-0156*	Reblozyl (luspatercept)	Revised
November 29, 2021	ING-CC-0124	Keytruda (pembrolizumab)	Revised
November 29, 2021	ING-CC-0104*	Levoleucovorin Agents	Revised
November 29, 2021	ING-CC-0062	Tumor Necrosis Factor Antagonists	Revised
November 29, 2021	ING-CC-0009*	Lemtrada (alemtuzumab) for the Treatment of Multiple Sclerosis	Revised
November 29, 2021	ING-CC-0020	Tysabri (natalizumab)	Revised
November 29, 2021	ING-CC-0029*	Dupixent (dupilumab)	Revised
November 29, 2021	ING-CC-0038	Human Parathyroid Hormone Agents	Revised
November 29, 2021	ING-CC-0182*	Iron Agents	Revised
November 29, 2021	ING-CC-0075	Rituximab Agents for Non-Oncologic Indications	Revised
November 29, 2021	ING-CC-0096	Asparagine Specific Enzymes	Revised
November 29, 2021	ING-CC-0169	Phesgo (pertuzumab/trastuzumab/ hyaluronidase-zzxf)	Revised

NYE-NU-0373-21 October 2021

Effective date	Document number	*Clinical Criteria* title	New or revised
November 29, 2021	ING-CC-0193	Evkeeza (evinacumab)	Revised
November 29, 2021	ING-CC-0081*	Crysvita (burosumab-twza)	Revised

Email is the quickest and most direct way to receive important information from Empire BlueCross BlueShield HealthPlus.

To start receiving email from us (including some sent in lieu of fax or mail), submit your information using the QR code to the right or via our online form (**https://bit.ly/3zqQdYB**).

Pharmacy Management Drug Policy

SUBJECT: Rare Diseases Clinical Review Prior Authorization (CRPA)
POLICY NUMBER: Pharmacy-98
EFFECTIVE DATE: 1/15/21
LAST REVIEW DATE: 12/22/2021

If the member's subscriber contract excludes coverage for a specific service or prescription drug, it is not covered under that contract. In such cases, medical or drug policy criteria are not applied. Medical or drug policies apply to commercial, SafetyNet, and Health Care Reform products only when a contract benefit for the specific service exists.

DESCRIPTION:

A disease is considered rare if it affects less than 200,000 people in the United States. There are over 6,800 rare diseases and it is estimated that 25-30 million Americans live with a rare disease. The exact cause for many rare diseases remains unknown but it is believed that most are linked to a genetic mutation. Still, environmental factors may also play a role in some of these conditions. Considerable progress has been made in recent years to find ways to diagnose and treat rare diseases.

This policy is applicable to drugs that are included on a specific drug formulary. If a drug referenced in this policy is non-formulary, please reference the Non-Formulary Medication Exception Review Policy for review guidelines.

Approval time periods: Unless otherwise noted within individual drug criteria, approval time periods are defined under Policy Guidelines at the end of this policy

DRUG SPECIFIC POLICIES/CRITERIA:

Actimmune – Interferon Gamma-1B (Medical & Rx)

1. For the treatment of Chronic Granulomatous Disease
   a. The prescribing physician is an infectious disease specialist or a hematologist/oncologist
   b. Diagnosis has been confirmed through neutrophil function tests
   c. Combination therapy with antibiotics (i.e., trimethoprim/sulfamethoxazole) and/or antifungals (i.e., itraconazole) has been shown to reduce the risk of severe infections.
2. In the treatment of severe, malignant osteopetrosis
   a. The prescribing physician is an orthopedic surgeon, hematologist, or an endocrinologist
   b. The diagnosis is confirmed through radiological evidence.
3. Approved dosing for those with a body surface area greater than 0.5 m^2 is 50 mcg/m^2 (1 million units/m^2) subcutaneously 3 times a week.
4. Doses above 50 mcg/m^2 will not be authorized.

Adagen-pegademase bovine – (Rx)

1. Must have a diagnosis of ADA-SCID confirmed by the following
   a. Absent or very low (< 1% of normal) adenosine deaminase (ADA) catalytic activity in plasma, urine, or dried blood spots prior to the initiation of enzyme replacement therapy **OR**
   b. Molecular genetic testing confirming bi-allelic mutations in the ADA gene
2. Must be prescribed by or in consultation with an immunologist, hematologist/oncologist or a physician that specializes in the treatment of ADA- SCID
3. Must have elevated deoxyadenosine triphosphate (dATP) levels or total deoxyadenosine (dAdo) nucleotides in erythrocytes (red blood cells) compared to a laboratory standard,

4. Patient must not be a suitable candidate for hematopoietic cell transplantation (HCT) at the time of the request OR patient has failed HCT
5. Adagen is dosed based on patient weight; therefore, current body weight and requested dose regimen must be submitted for initial review and each recertification request
6. Initial approval will be for one year.
7. Recertification every two years thereafter will require documentation of a positive response to treatment such as one or more of the following:
    a. Improvement in immune status (total lymphocyte and B, T, and natural killer (NK) lymphocyte counts, quantitative immunoglobulin (Ig) concentration [IgG, IgA, IgM])
    b. Improvement in clinical status (infection rate, incidence and duration of hospitalization, and performance status)
    c. Normalization of plasma ADA activity, erythrocyte dATP or total dAdo nucleotide levels compared to a laboratory standard

Recommended Dosing:

- A maximum single dose of 30 U/kg should not be exceeded per FDA approved labeling Adagen is administered every 7 days as an intramuscular injection. 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.

Aldurazyme- laronidase (Medical)

1. Must have a diagnosis of Hurler, Hurler-Scheie or Scheie form of MPS I confirmed by biochemical enzyme analysis for alpha-L-iduronidase enzyme deficiency in white blood cells or cultured skin fibroblasts
2. Patient must be followed by a physician experienced in metabolic disorders
3. Must have an affected 1st degree relative OR have clinical symptoms of the disease such as: Valvular heart disease, cardiomyopathy, obstructive sleep apnea, restrictive lung disease, reactive airway disease, joint stiffness, joint contractures, joint pain, spinal deformities, corneal clouding, glaucoma, developmental delay, mental retardation, communicating hydrocephalus, hearing loss, hepatomegaly, inguinal/umbilical hernia, and chronic infections
4. Must be ≥6 months of age
5. Current body weight and requested dose regimen must be submitted for initial review and each recertification request

Recommended Dosing:

- 0.58 mg/kg IV infusion once weekly

HCPCS: J1931

Arcalyst - rilonacept (Rx)

1. Must have a diagnosis of Cryopyrin-Associated Periodic Syndromes (CAPS) with one ofthe following conditions: Familial Cold Autoinflammatory Syndrome (FCAS) also known as Familial Cold Urticaria ORMuckle-Wells Syndrome (MWS) **AND**
    a. Patient must be at least 12 years of age
    b. Patient is not on concurrent therapy with any of the following – Ilaris, Kineret, Enbrel, Humira, infliximab or Simponi
    c. The recommended dose for CAPS, FCAS, MWS
        i. Adults: Loading dose: 320 mg, delivered as two 160 mg (2 mL) injections. Maintenance dose: 160 mg (2 mL) injection once weekly.
        ii. Pediatric patients 12 years to 17 years: Loading dose: 4.4 mg/kg, up to a maximum of 320 mg, delivered as 1 or 2 injections (not to exceed 2 mL/injection). Maintenance dose: 2.2 mg/kg, up to a maximum of 160 mg (2 mL) injection, once weekly.

d. **Note** – it is not known whether Arcalyst is effective in patients with Neonatal-Onset Multisystem Inflammatory Disease (NOMID), also referred to as Chronic Infantile Neurologic CutaneousArticular Syndrome (CINCA). **OR**

2. Must have a diagnosis of Deficiency of Interleukin-1 Receptor Antagonist (DIRA) confirmed by mutation in the *IL1RN* gene **AND**
   a. Must be prescribed by or in consultation with a rheumatologist, geneticist, dermatologist, or a physician specializing in the treatment of autoinflammatory conditions **AND**
   b. Patient must weigh at least 10 kg **AND**
   c. According to the prescriber, the patient has demonstrated clinical benefit with Kineret (anakinra subcutaneous injection). Examples of clinical benefit include: resolution of skin rash, bone pain, and fever, normal acute phase reactants (CRP<0.5 mg/dL), objective absence of skin rash, no radiological evidence of active bone disease, reduction in the use of corticosteroids **AND**
   d. Patient is not on concurrent therapy with any of the following – Ilaris, Kineret, Enbrel, Humira, infliximab or Simponi
   e. The recommended dose of Arcalyst for DIRA is as follows:
      i. Adult and pediatric patients weighing at least 10 kg: 4.4 mg/kg up to a maximum of 320 mg delivered as 1 or 2 injections (2 mL/injection) once weekly **OR**
3. Must have diagnosis of recurrent pericarditis (RP) defined as a subsequent pericarditis episode after a symptom-free interval of at least 4-6 weeks
   a. Must be prescribed by or in consultation with a cardiologist **AND**
   b. Patient must be ≥ 12 years or older **AND**
   c. Patient must have had ≥ 1 prior episode of pericarditis that met two or more of the following:
      i. Pericarditis chest pain (typically sharp chest pain, improved with sitting up and leaning forward)
      ii. Pericardial rubs (superficial scratchy or squeaking sound heard with the diaphragm of a stethoscope over the left sternal border)
      iii. New widespread ST-elevation or PR depression on ECG
      iv. Pericardial effusion (new or worsening) **AND**
   d. Patient must be presenting with at least a second pericarditis recurrence (third pericarditis episode at minimum) despite treatment with NSAIDs, colchicine or corticosteroids, in any combination
      i. The current episode is characterized by pericardial pain for ≥ 1 day with a numerical rating scale (NRS) pain score of ≥ 4 AND a C-reactive protein level of at least of at least 1 mg/dL **OR**
      ii. The current episode must have met two or more of the following:
         A. Pericarditis chest pain (typically sharp chest pain, improved with sitting up and leaning forward)
         B. Pericardial rubs (superficial scratchy or squeaking sound heard with the diaphragm of a stethoscope over the left sternal border)
         C. New widespread ST-elevation or PR depression on ECG
         D. Pericardial effusion (new or worsening) **AND**
   e. Provider must attest that the patient will attempt to taper and discontinue NSAIDs, colchicine and/or corticosteroids while on Arcalyst **AND**
   f. Arcalyst will not be approved for patients with pericarditis secondary to tuberculosis, post-thoracic blunt trauma, myocarditis, systemic autoimmune diseases (excluding Still's disease), or neoplastic, purulent, or radiation etiologies **AND**
   g. Arcalyst will not be approved for patients with incessant or chronic pericarditis **AND**

h. Patient is not on concurrent therapy with any of the following – Ilaris, Kineret, Enbrel, Humira, infliximab or Simponi
i. The recommended dose for RP is as follows:
    i. Adults: Loading dose: 320 mg, delivered as two 160 mg (2 mL) injections. Maintenance dose: 160 mg (2 mL) injection once weekly.
    ii. Pediatric patients 12 years to 17 years: Loading dose: 4.4 mg/kg, up to a maximum of 320 mg, delivered as 1 or 2 injections (not to exceed 2 mL/injection). Maintenance dose: 2.2 mg/kg, up to a maximum of 160 mg (2 mL) injection, once weekly.
j. Initial approval of Arcalyst for recurrent pericarditis will be for 3 months. Recertification will require documentation that the patient has had no pericarditis recurrence while using Arcalyst AND documentation that NSAIDs, colchicine and/or corticosteroid doses have been reduced or discontinued.

4. Quantity limit of 4 vials/28 days
    a. The allowed quantity will be reviewed in accordance with FDA-approved weight and age-based dosing and, as such, will be limited to the minimum number of vials to obtain the appropriate weekly dose.
    b. A one-time override of 5 vials per 28 days will be allowed for diagnosis of CAPs, FCAS, MWS and RP to accommodate for the loading dose. A quantity limit exception (8 vials/28 days) can be granted for diagnosis of DIRA requiring 2 injections administered once weekly.

Bylvay-odevixibat (Rx)

1. Must be ≥ 3 months of age **AND**
2. Must be prescribed by a hepatologist, gastroenterologist, or physician knowledgeable in the management of progressive familial intrahepatic cholestasis (PFIC) **AND**
3. Must have a diagnosis of PFIC types 1-6, confirmed by molecular genetic testing **AND**
4. Must have a serum bile acid concentration that exceeds the upper limit of normal **AND**
5. Provider attestation or documentation that the patient is experiencing significant pruritis
6. Bylvay oral pellets are intended for patients weighing < 19.5 kg and Bylvay capsules are intended for patients weighing ≥ 19.5 kg
7. The recommended dosage is 40 mcg/kg once daily in the morning with a meal. If there is no improvement in pruritus after 3 months, the dosage may be increased in 40 mcg/kg increments up to 120 mcg/kg once daily, not to exceed a total daily dose of 6 mg.
8. Initial approval will be for 6 months. Recertification will require documentation that the patient is tolerating therapy and is experiencing a decrease in pruritis from baseline and/or decrease in serum bile acid concentration. Recertification will be required every 12 months.
    a. Bylvay may not be effective in PFIC type 2 patients with ABCB11 variants resulting in non-functional or complete absence of bile salt export pump protein (BSEP-3).
9. Quantity limit of 30 /30 days for oral pellets and capsules
    a. Upon each drug review and dose escalation request, the allowed quantity will be reviewed in accordance with the FDA-approved weight-based dosing (see table 1) and, as such, will be limited to the minimum number of oral pellets or capsules of each strength to obtain the appropriate daily dose.

Table 1. Recommended Dosage for 40 mcg/kg/day

Body Weight (kg)	Total Daily Dose (mcg)
7.4 and below	200
7.5 to 12.4	400
12.5 to 17.4	600
17.5 to 25.4	800
25.5 to 35.4	1200
35.5 to 45.4	1600
45.5 to 55.4	2000
55.5 and above	2400

Cuprimine and generic penicillamine capsules (Rx)

1. Must be used for an FDA approved indication: Wilson's Disease, Rheumatoid Arthritis or Cystinuria **AND**
2. Based on comparable indications, efficacy, safety profiles and dosing, penicillamine tablets (the generic for Depen) will be required unless there is adequate justification by the prescriber as to why penicillamine tablets are not clinically appropriate **AND**
3. Requests for brand Cuprimine will require documentation of serious side effects or drug failure with generic penicillamine capsules (generic Cuprimine)
4. Quantity limit: 180 capsules/30 days.
    a. A quantity limit exception of 480 capsules/30 days can be granted for a diagnosis of Cystinuria
    b. A quantity limit exception of 240 capsules /30 days can be granted for a diagnosis of Wilson's Disease

Empaveli— pegcetacoplan (Medical)

1. Must be 18 years of age or older **AND**
2. Must be prescribed by a hematologist or nephrologist **AND**
3. Must have a diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) confirmed by a flow cytometry test
4. The recommended dose of Empaveli is 1,080 mg by subcutaneous infusion twice weekly via a commercially available infusion pump. For lactate dehydrogenase (LDH) levels greater than 2 × the upper limit of normal (ULN), adjust the dosing regimen to 1,080 mg every three days.
    a. For patients switching from Soliris (eculizumab), initiate Empaveli while continuing Soliris (eculizumab) at its current dose. After 4 weeks, discontinue Soliris (eculizumab) before continuing on monotherapy with Empaveli.
    b. For patients switching from Ultomiris (ravulizumab), initiate Empaveli no more than 4 weeks after the last dose of Ultomiris (ravulizumab)
5. Initial approval for 6 months. Continued approval will be for 1 year and will require documentation that patient is tolerating therapy and is responding to treatment (i.e., decrease in number of transfusions, improvement in hemoglobin levels, normalization of LDH levels, symptom improvement)
6. Concomitant use of another complement inhibitor (i.e., Soliris (eculizumab) or Ultomiris (ravulizumab) will only be authorized for patients transitioning from either Soliris (eculizumab) or Ultomiris (ravulizumab) to Empaveli. After the initial approval period, requests for concomitant use of Empaveli with Soliris (eculizumab) or Ultomiris (ravulizumab) will be considered experimental/investigational and will not be approved.

7. Quantity limit: 8 vials per 30 days. A quantity limit exception of 10 vials per 30 days may be granted for individuals requiring 1,080 mg dosed every three days.

Enspryng – satralizumab-mwge injection (Rx or Medical)

1. Must have a diagnosis of Neuromyelitis Optica Spectrum Disorder (NMOSD) confirmed by a positive anti-aquaphorin-4 (AQP4) antibody test
2. Must be at least 18 years of age
3. Must be prescribed by an ophthalmologist or neurologist
4. Must have had at least 1 neuromyelitis optica relapse that required rescue therapy (such as corticosteroids or plasma exchange) in the last 12 months
5. Enspryng will be covered under the pharmacy benefit for self-injection unless there is documentation of an inability to self-inject and lack of a caregiver available to inject. With documentation of an inability to self-inject and lack of an available caregiver to inject, coverage under the medical benefit will be considered with the same clinical criteria above.
6. Quantity Limit of 1 syringe (1 mL) per 28 days
    a. Coverage of an initial loading dose of 3 syringes (3 mL) per 28 days will be authorized for the first 4 weeks of treatment
    b. Please see the package insert for recommendations regarding delayed or missed doses.

Evkeeza-evinacumab-dgnb (Medical)

1. Must be prescribed by or in consultation with a cardiologist, lipid specialist, or endocrinologist **AND**
2. Must be $\underline{\geq}$ 12 years of age or older with a diagnosis of homozygous familial hypercholesterolemia (HoFH) **AND**
    a. Genetic testing must demonstrate evidence of two mutant alleles at the low-density lipoprotein receptor (*LDLR*), apolipoprotein B (*APOB*), proprotein convertase subtilisin kexin type 9 (*PCSK9*) or low-density lipoprotein receptor adaptor protein 1 (*LDLRAP1*) gene **OR**
    b. Patient has a history of untreated LDL-C > 500 mg/dL or treated LDL-C $\underline{\geq}$ 300 mg/dL with either (i or ii)
        i. Xanthoma before the age of 10 years **OR**
        ii. Evidence of heterozygous FH in both parents **AND**
3. Patient must have failed to reach target LDL-C while receiving treatment with high-intensity statin therapy (i.e., atorvastatin 80 mg/day or rosuvastatin 40 mg/day), or maximally tolerated statin therapy, in combination with ezetimibe and a PCSK9 inhibitor (i.e., Praluent, Repatha) for at least 8 weeks:
    a. LDL-C must be $\underline{\geq}$ 70 mg/dL for patients with clinical atherosclerotic cardiovascular disease (ASCVD) **OR** LDL-C must be $\underline{\geq}$ 100 mg/dL for patients without documented clinical ASCVD
        i. Clinical ASCVD defined as having a history of acute coronary syndrome, myocardial infarction (MI), stable or unstable angina, coronary/other arterial revascularization, stroke, TIA, peripheral arterial disease, or other documented atherosclerotic disease (such as coronary atherosclerosis, renal atherosclerosis, aortic aneurysm secondary to atherosclerosis, or Carotid plaque with ≥ 50% stenosis)
    b. If patient is known to have two LDL-receptor negative alleles (null homozygous) then trial of PCSK9 inhibitor is not required
    c. Evkeeza will not be approved in combination with Juxtapid unless the patient has demonstrated failure to achieve target LDL-C while on Juxtapid in combination with:
        i. a high-intensity or maximally tolerated statin therapy **AND**
        ii. ezetimibe **AND**

iii. a PCSK9 inhibitor (i.e., Praluent, Repatha) **AND**
iv. The patient has been on this drug combination for at least 8 weeks

d. If patient is unable to tolerate statin therapy, documentation in progress notes must include:
i. A contraindication to statin therapy according to FDA labeling **OR**
ii. History of statin-related rhabdomyolysis
1. Must have symptoms consistent with rhabdomyolysis (i.e., muscle pain, swelling, and weakness, dark urine) **AND**
2. Must have creatine kinase (CK) level > 10 times upper limit of normal, myoglobinuria, or acute renal failure (increase in serum creatinine >0.5 mg/dL) **AND**
3. Patient was receiving a statin at the time of the event and symptoms resolved upon discontinuation of the statin **OR**
iii. History of statin intolerance. Documentation must include the following:
1. Inability to tolerate at least 2 different statins
a. At least 1 statin must be hydrophilic (such as pravastatin, fluvastatin or rosuvastatin) starting at the lowest starting average daily dose **AND**
b. Intolerance associated with confirmed, intolerable statin-related adverse effects (i.e., muscle related symptoms) or significant biomarker abnormalities (i.e., ALT/AST > 3 times the upper limit of normal accompanied by increase in total bilirubin > 2 times the upper limit of normal) **AND**
c. Non-statin causes of muscle symptoms or biomarker abnormalities have been ruled out (for example, hypothyroidism, reduced renal function, reduced hepatic function, rheumatologic disorders such as polymyalgia rheumatic, steroid myopathy, vitamin D deficiency, or primary muscle disease)

4. Documentation of baseline LDL-C level must be provided-measurement must occur within 60 days prior to treatment **AND**
5. Provider must attest that a discussion with the patient has taken place regarding a heart healthy diet, the importance of exercise, and smoking cessation (if applicable)
6. The recommended dosage is 15 mg/kg administered by intravenous (IV) infusion every 4 weeks
7. Evkeeza will not be approved for other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH)
8. Evkeeza will be covered under the medical benefit
9. Initial approval will be for 6 months, further approval will require evidence of an adequate reduction in LDL-C level defined as reduction in LDL-C level as compared to baseline LDL-C. Recertification will be yearly after that.

HCPCS: J1305

Exservan and Tiglutik -riluzole oral film and oral suspension (Rx)

1. Must be ≥ 18 years of age **AND**
2. Must be prescribed by or in consultation with a neurologist, or provider that specializes in Amyotrophic Lateral Sclerosis (ALS) **AND**
3. Must have a diagnosis of ALS **AND**
4. Provider must attest that patient is unable to swallow generic riluzole tablets
5. Quantity Limit: 60 oral films/30 days and 600 mL/30 days

Firdapse-amifampridine (Rx)

1. Must be prescribed by a neurologist or neuromuscular specialist
2. Must be 18 years of age or older
3. Must have a diagnosis of Lambert-Eaton Myasthenic Syndrome (LEMS) confirmed by electromyography OR calcium channel antibody testing
4. Based on comparable indications, efficacy, safety profiles and equivalent formulation and strength Ruzurgi will be the required amifampridine product unless there is adequate justification by the prescriber as to why Ruzurgi is not clinically appropriate
5. Quantity limit 250 tablets per 30 days

Gamifant-emapalumab-lzsg (Medical)

1. Prescribed by a physician who specializes in the treatment of HLH (such as a hematologist, oncologist, immunologist, or transplant specialist) **AND**
2. The patient has a diagnosis of Primary HLH confirmed by at least one of the following (either i., ii., or iii)
   i. Genetic testing confirming biallelic pathogenic variants (e.g., PRF1, UNC13D/MUNC13-4, STX11 or STXBP2) **OR**
   ii. Positive family history (affected siblings or parental consanguinity) consistent with primary HLH in a symptomatic individual **OR**
   iii. Meet at least FIVE out of the following diagnostic criteria prior to treatment:
      A. Low or absent NK-cell activity (according to local laboratory reference)
      B. Fever ≥ 38.5°C (or 101.3°F)
      C. Splenomegaly
      D. Elevated ferritin ≥ 500 micrograms/L
      E. Elevated CD25 (i.e., soluble IL-2 receptor) ≥ 2,400 U/mL
      F. Hypertriglyceridemia (fasting triglycerides ≥ 265 mg/dL (3 mmol/L) and/or hypofibrinogenemia (fibrinogen ≤ 1.5g/L)
      G. Hemophagocytosis in bone marrow or spleen or lymph nodes
      H. Cytopenias affecting at least 2 of 3 lineages in the peripheral blood:
         - Hemoglobin < 9 g/dL (or < 10g/dL in infants < 4 weeks of age)
         - Platelets < 100 x 10^9/L
         - Neutrophils < 1 x 10^9/L, **AND**
3. Evidence of active disease that is refractory, recurrent, or progressive despite at least ONE conventional HLH therapy **OR** severe intolerance to at least ONE conventional therapy. Examples of conventional HLH treatments include etoposide and dexamethasone, cyclosporine A, anti-thymocyte globulin and intrathecal methotrexate following a standard of care treatment protocol **AND**
4. Administer dexamethasone concomitantly with Gamifant, **AND**
5. Administer Gamifant until hematopoietic stem cell transplantation (HSCT) is performed or unacceptable toxicity. Discontinue Gamifant when patient no longer requires therapy for the treatment of HLH.
6. Prior authorization for Gamifant will apply regardless of the site of administration (applies to both the inpatient and outpatient setting). Gamifant must be administered by a healthcare professional and is covered under the medical benefit **AND**
7. Gamifant is dosed based on body weight. Therefore, current body weight and requested dose regimen must be submitted for initial review and each recertification request **AND**
8. Initial approval will be for 2-month duration
9. Continuation of therapy at 2-month intervals will require the following documentation of therapeutic benefit:

a. Complete response defined as normalization of all HLH abnormalities (i.e., no fever, no splenomegaly, neutrophils > $1x10^9$/L, platelets > $100x10^9$/L, ferritin < 2,000 ug/L, fibrinogen > 1.50 g/L, D-dimer < 500 ug/L, normal CNS symptoms, no worsening of sCD25 > 2-fold baseline); **OR**
b. Partial response defined as normalization of ≥ 3 HLH abnormalities, **OR**
c. HLH improvement defined as ≥ 3 HLH abnormalities improved by at least 50% from baseline

Recommended Dosing:

- 1mg/kg twice per week via IV infusion. Dose may be increased based on clinical and laboratory findings up to a maximum dose of 10mg/kg

HCPCS: J9210

Ilaris - canakinumab (Medical)

1. Must be at least 4 years of age and have a diagnosis of Cryopyrin-Associated Periodic Syndromes (CAPS) with one of the following conditions
   a. Familial Cold Autoinflammatory Syndrome (FCAS) also known as Familial Cold Urticaria **OR**
   b. Muckle-Wells Syndrome (MWS)
   c. Dose is not to exceed 150mg every 8 weeks **OR**
2. Must be at least 2 years of age with a diagnosis of active systemic juvenile idiopathic arthritis (SJIA)
   a. Must have failed to respond to and/or is intolerant to glucocorticoids or methotrexate **AND**
   b. Must have failed to respond to and/or is intolerant to Enbrel or Humira.
   c. Dose is not to exceed 300mg every 4 weeks **OR**
3. Must be at least 18 years of age with a diagnosis of Adult-Onset Still's Disease (AOSD)
   a. Must have failed to respond to and/or is intolerant to glucocorticoids or methotrexate **AND**
   b. Must have failed to respond to and/or is intolerant to a TNF inhibitor (i.e., infliximab, Enbrel (etanercept) or Humira (adalimumab)), or there is a medical reason why the patient cannot use a TNF inhibitor.
   c. Dose is not to exceed 300mg every 4 weeks **OR**
4. Must be at least 2 years of age with a diagnosis of one of the following Periodic Fever Syndromes (Hereditary Periodic Fevers)
   a. Tumor Necrosis Factor-Receptor Associated Periodic Syndrome (TRAPS)
   b. Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD)
   c. Familial Mediterranean Fever (FMF)
   d. Dose is not to exceed 300mg every 4 weeks.
5. Patient does not have an infection and is not at high risk for infection
6. Patient is not on concurrent therapy with any of the following – Arcalyst, Kineret, Enbrel, Humira, infliximab or Simponi

Note – it is not known whether Ilaris is effective in patients with Neonatal-Onset Multisystem Inflammatory Disease (NOMID), also referred to as Chronic Infantile Neurologic Cutaneous Articular Syndrome (CINCA).

HCPCS: J0638

Increlex - mecasermin, Recombinant, rh-IGF-1 (Rx)

1. Must be prescribed by an endocrinologist or pediatric endocrinologist
2. Patient must be 2 years old or greater
3. Patient must have severe primary IGF-1 deficiency (Primary IGFD) defined as:
   a. height standard deviation score ≤ -3.0
   b. basal IGF-1standard deviation score ≤ -3.0
   c. normal or elevated GH **OR**
4. Patient must have growth hormone (GH) gene deletion with the development of neutralizing antibodies to GH

5. Normal dose of 40-120mcg/kg SQ twice daily given 20 minutes before or after a meal or snack to avoid hypoglycemia. Doses greater than 120mcg/kg will not be covered
6. Increlex will not be covered for growth promotion in patients with closed epiphyses or as a substitute for growth hormone replacement therapy.

Isturisa – osilodrostat tablets (Rx)

1. Must be 18 years of age or older
2. Must be prescribed by an endocrinologist
3. Must have a diagnosis of Cushing's Disease
4. Must have a mean urinary free cortisol (UFC) level that is at least 1.5x the upper limit of normal measured over three 24 hour measurements (ULN = 50 micrograms/24 hours or 145 nmol/24 hours)
5. Must have documentation of symptoms of Cushing's Disease (such as diabetes, central obesity, moon face, buffalo hump, osteoporosis, muscle wasting, hypertension, depression, and anxiety)
6. Must have documentation of a failed pituitary surgery or contraindication to pituitary surgery
7. Must have had serious side effects or drug failure with Signifor.
8. Other causes of Cushing's Syndrome aside from Cushing's Disease (which is specifically caused by a pituitary adenoma) will be excluded from coverage.
9. Initial approval will be for 3 months. Recertification at 3 months and thereafter will require laboratory results to document a recent UFC level within normal limits **AND** improvement in the symptoms of Cushing's Disease.
10. For recertification, the prescriber must also make clear the maintenance dose they are planning to use. Approval will be allowed for this amount for 1 year.
11. Dose increases beyond the initial 3 months will require documentation to show UFC levels above the upper limit of normal and documentation that the patient is still experiencing Cushing's Disease symptoms. If approved, dose increase authorizations will be for 1 year and will allow the amount requested only.
12. Dosing must be in accordance with FDA labeling, starting at 2 mg twice daily, and increased by 1 mg or 2 mg twice daily, no more frequently than every 2 weeks based on the rate of cortisol changes, individual tolerability, and improvement in signs and symptoms.
13. Please see the Isturisa Efficient Dosing chart at the bottom of this document (Figure 1A) for information on the number of tablets allowed per 30 days of each strength for a given dosing.

Juxtapid – lomitapide capsules (Rx)

1. Must be prescribed by or in consultation with a cardiologist, lipid specialist or endocrinologist **AND**
2. Must be ≥18 years of age with a diagnosis of homozygous familial hypercholesteremia **AND**
    a. Genetic testing must demonstrate evidence of two mutant alleles at the low-density lipoprotein receptor (*LDLR*), apolipoprotein B (*APOB*), proprotein convertase subtilisin kexin type 9 (*PCSK9*) or low-density lipoprotein receptor adaptor protein 1 (*LDLRAP1*) gene **OR**
    b. Patient has a history of untreated LDL-C > 500 mg/dL or treated LDL-C ≥ 300 mg/dL with either (i or ii)
        i. Xanthoma before the age of 10 years **OR**
        ii. Evidence of heterozygous FH in both parents **AND**
3. Patient must have failed to achieve LDL-C goal despite previous concurrent use of:
    a. High-intensity statin therapy (atorvastatin 80mg/day or rosuvastatin 40mg/day), or maximally tolerated statin, concurrently with ezetimibe **OR**
    b. High-intensity statin therapy (atorvastatin 80mg/day or rosuvastatin 40mg/day), or maximally tolerated statin, with apheresis **AND**
4. LDL-C must be ≥ 70 mg/dL for patients with clinical atherosclerotic cardiovascular disease (ASCVD) **OR** LDL-C must be ≥ 100 mg/dL for patients without documented clinical ASCVD

   a. Clinical ASCVD defined as having a history of acute coronary syndrome, myocardial infarction (MI), stable or unstable angina, coronary/other arterial revascularization, stroke, TIA, peripheral arterial disease, or other documented atherosclerotic disease (such as coronary atherosclerosis, renal atherosclerosis, aortic aneurysm secondary to atherosclerosis, or Carotid plaque with ≥ 50% stenosis)
5. If patient is unable to tolerate statin therapy, documentation in progress notes must include:
   a. A contraindication to statin therapy according to FDA labeling **OR**
   b. History of statin-related rhabdomyolysis
      i. Must have symptoms consistent with rhabdomyolysis (i.e., muscle pain, swelling, and weakness, dark urine) **AND**
      ii. Must have creatine kinase (CK) level > 10 times upper limit of normal, myoglobinuria, or acute renal failure (increase in serum creatinine >0.5 mg/dL) **AND**
   c. Patient was receiving a statin at the time of the event and symptoms resolved upon discontinuation of the statin **OR**
   d. History of statin intolerance. Documentation must include the following:
   e. Inability to tolerate at least 2 different statins
      i. At least 1 statin must be hydrophilic (such as pravastatin, fluvastatin or rosuvastatin) starting at the lowest starting average daily dose **AND**
      ii. Intolerance associated with confirmed, intolerable statin-related adverse effects (i.e., muscle related symptoms) or significant biomarker abnormalities (i.e., ALT/AST > 3 times the upper limit of normal accompanied by increase in total bilirubin > 2 times the upper limit of normal) **AND**
      iii. Non-statin causes of muscle symptoms or biomarker abnormalities have been ruled out (for example, hypothyroidism, reduced renal function, reduced hepatic function, rheumatologic disorders such as polymyalgia rheumatic, steroid myopathy, vitamin D deficiency, or primary muscle disease)
6. Must have had trial and failure/intolerance to a PCSK9 inhibitor (i.e., Praluent, Repatha) when used in combination with a maximally tolerated statin plus ezetimibe
   a. If patient is known to have two LDL-receptor negative alleles (null homozygous) then trial of PCSK9 inhibitor is not required
7. Documentation of baseline LDL-C level must be provided-measurement must occur within 60 days prior to treatment **AND**
8. Provider must attest that a discussion with the patient has taken place regarding a heart healthy diet, the importance of exercise, and smoking cessation (if applicable)
9. Initial approval will be for 8 weeks. Further approval will require evidence of an adequate reduction in LDL-C level defined as reduction in LDL-C level as compared to baseline LDL-C. Recertification will be required yearly thereafter.
10. Juxtapid will not be approved in combination with Evkeeza unless the patient has demonstrated failure to achieve target LDL-C while on Evkeeza in combination with:
    a. high-intensity or maximally tolerated statin therapy **AND**
    b. ezetimibe **AND**
    c. a PCSK9 inhibitor (i.e., Praluent, Repatha) **AND**
    d. the patient has been on this drug combination for at least 6 months.
11. Quantity limit of 28 capsules per 28 days for 5 mg and 10 mg and 56 capsules per 28 days for 20 mg and 30 mg strengths

Keveyis – dichlorphenamide (Rx)

1. Diagnosis must be made by a neurologist or muscle disease specialist.
2. Member must have a diagnosis of primary hypokalemic periodic paralysis **AND**
   a. The diagnosis must be confirmed by **BOTH** of the following:
      - A genetic test confirming a skeletal muscle calcium or sodium channel mutation **AND**
      - Serum potassium concentration of less than 3.5 mEq/L during a paralytic attack
   b. Must have had trial and failure with prescription potassium supplementation **AND**
   c. The patient must have had a trial with oral acetazolamide therapy that did not result in improvement in severity or frequency of attacks **OR**
3. Member must have a diagnosis of primary hyperkalemic periodic paralysis **AND**
   a. The diagnosis must be confirmed by **BOTH** of the following:
      - A genetic test confirming a skeletal muscle sodium channel mutation **AND**
      - Serum potassium concentration of greater than 5.0 mEq/L during a paralytic attack **AND**
   b. The patient must have had a trial with oral acetazolamide therapy that did not result in improvement in severity or frequency of attacks
4. For hypokalemic or hyperkalemic periodic paralysis, initial approval will be for 2 months. Recertification will require a documented improvement in the frequency or severity of attacks while taking Keveyis. Recertification will be approved for 1 year
5. Initial dosing is one 50 mg tablet twice daily. Keveyis can be titrated up to a maximum of 200mg daily.
6. Quantity limit of 120 tablets per 30 days

Korlym – mifepristone tablets (Rx)

1. Member must have a diagnosis of endogenous Cushing's syndrome
2. Must also have a diagnosis of type 2 diabetes mellitus or glucose intolerance
3. Must have failed surgery or is not a candidate for surgery
4. Must be prescribed by an endocrinologist
5. Patients who meet the criteria for approval for treatment with Korlym will be approved for 12 months. Recertification will require patients to have stabilization/decrease in A1C or objective clinical response.
6. Recommended initial dosing is 300mg once daily with a meal.
7. Increase in 300mg increments to a maximum of 1200mg once daily based on clinical response and tolerability. Do not exceed 20mg/kg per day.
8. Quantity limit of 120 tablets per 30 days.

Livmarli—maralixibat (Rx)

1. Must be ≥ 1 year of age **AND**
2. Must be prescribed by a hepatologist, gastroenterologist, or physician knowledgeable in the management of Alagille syndrome (ALGS) **AND**
3. Must have a diagnosis of Alagille syndrome, confirmed by molecular genetic testing (JAG1 or NOTCH2 mutation) **AND**
4. Must have evidence of cholestasis defined as at least one of the following:
   a. Total serum bile acid > 3x upper limit of normal (ULN) for age
   b. Conjugated bilirubin > 1 mg/dL
   c. Fat soluble vitamin deficiency otherwise unexplainable
   d. Gamma Glutamyl Transferase (GGT) > 3x ULN for age
   e. Intractable pruritus explainable only by liver disease **AND**
5. Provider attestation or documentation that the patient is experiencing significant pruritis

6. Initial approval will be for 6 months. Recertification will require documentation that the patient is tolerating therapy and is experiencing a decrease in pruritis from baseline and/or decrease in serum bile acid concentration from baseline. Recertification will be required every 12 months.
7. Quantity limit of 30 mL/30 days
    a. Upon each drug review and dose escalation request, the allowed quantity will be reviewed in accordance with the FDA-approved weight-based dosing (see table 1) and, as such, will be limited to the minimum number of whole bottles to obtain the appropriate daily dose/day supply.
    b. Quantity approvals will be added to allow for dispensing of the whole bottle size needed (30 mL)

Table 1: Individual Dose Volume by Patient Weight

Patient Weight (kg)	Days 1-7 (190 mcg/kg once daily)		Beginning Day 8 (380 mcg/kg once daily)	
	Volume QD (mL)	Dosing dispenser size (mL)	Volume QD (mL)	Dosing dispenser size (mL)
5 to 6	0.1	0.5	0.2	0.5
7 to 9	0.15		0.3	
10 to 12	0.2		0.45	
13 to 15	0.3		0.6	1
16 to 19	0.35		0.7	
20 to 24	0.45		0.9	
25 to 29	0.5		1	
30 to 34	0.6	1	1.25	3
35 to 39	0.7		1.5	
40 to 49	0.9		1.75	
50 to 59	1		2.25	
60 to 69	1.25	3	2.5	
70 or higher	1.5		3	

Luxturna – voretigene neparvovec-rzyl (Medical)

1. Must be prescribed by an ophthalmic surgeon for administration at a certified treatment center **AND**
2. Must be ≥ 12 months of age based upon ongoing cell proliferation in those under 1 year of age **AND**
3. Must have a diagnosis of Biallelic RPE65 mutation-associated retinal dystrophy
    a. Diagnosis must be confirmed by genetic testing **AND**
4. Patient must have viable retinal cells
    b. Viable retinal cells must have been determined by retinal thickness on spectral domain optical coherence tomography (OCT >100 microns within the posterior pole) **AND**
5. Baseline full-field light sensitivity threshold (FST) test results for each eye must be submitted
6. A maximum of 1 dose of 1.5 x 1011 vector genonomes (vg) administered by subretinal injection in a total volume of 0.3 mL will be allowed per eye per lifetime

HCPCS: J3398

Myalept - metreleptin (Rx)

1. Diagnosis of either congenital or acquired generalized lipodystrophy **AND** at least one of the following co-morbidities: diabetes mellitus, hypertriglyceridemia, and/or increased fasting insulin
2. A1C > 7% despite adequate drug therapy (trial of combination diabetic drug therapy) **OR** triglycerides > 200 mg/dL despite adequate drug therapy (trial of a high dose statin and a fibrate agent).
3. Initial approval will be for 4 months. Initial recertification approval will require documentation of an improvement in A1C of at least 1 percentage point and/or an improvement in triglycerides of at least 20%. Subsequent approvals will require documentation of maintained triglyceride/ A1C improvement.
4. Treatment with metreleptin is contraindicated in patients with general obesity not associated with congenital leptin deficiency and will not be authorized
5. Treatment with metreleptin for HIV associated lipodystrophy will not be authorized

Procysbi - cysteamine capsules and packets (Rx)

1. Drug must be prescribed a nephrologist or genetic specialist. **AND**
2. Patient must have a diagnosis of nephropathic cystinosis **AND**
3. Procysbi will not be approved for patients with hypersensitivity to penicillamine **AND**
4. Member must have had documented intolerability to Cystagon (immediate-release cysteamine). Intolerability is defined as severe nausea, vomiting, anorexia, fever, or lethargy that interferes with activity of daily living.
5. Based on comparable efficacy between the medications, Procysbi will not be authorized for those who fail to adhere to the standard Cystagon dosing regimen. The underlying cause of the non-adherence should be addressed and resolved.
6. Recommended maintenance dose is 1.3 gram/m^2/day in 2 divided doses, every 12 hours, recommended initial dosing in cysteamine-naïve patients is 1/6-1/4 of the maintenance dose of Procysbi.
7. Procysbi should be taken at least 2 hours after and at least 30 minutes before eating.
8. QL of 180/30 days for the 75mg capsules and 75 mg packets and 60/30 for the 25mg capsules and 300 mg packets. Upon each drug review and dose escalation request, the allowed quantity will be reviewed in accordance with the FDA-approved BSA-based dosing and, as such, will be limited to the minimum number of capsules or packets to obtain the appropriate daily dose.

Radicava – edaravone (Medical)

1. Must be greater than 18 years of age **AND**
2. Must be prescribed by or in consultation with a provider that specializes in Amyotrophic lateral sclerosis (ALS) and/or neuromuscular disorders **AND**
3. Must have a diagnosis of ALS
4. Recommended dosing is:
   a. 60mg administered as an IV infusion over 60 minutes.
   b. Initial treatment cycle: daily dosing for 14 days followed by a 14-day drug-free period

Subsequent treatment cycles: daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods.

HCPCS: J1301

Reblozyl-luspatercept-aamt (Medical)

Anemia in Adults with Beta Thalassemia

1. Must have a diagnosis of beta thalassemia (including HbE/beta thalassemia and beta thalassemia combined with alpha-thalassemia)
    i. Reblozyl will not be covered for any other diagnoses including alpha thalassemia and sickle cell beta thalassemia (also known as hemoglobin S/β-thalassemia)
    b. Must be at least 18 years of age
    c. Must be followed by a hematologist or physician knowledgeable in the treatment of beta-thalassemia
    d. Must require regular RBC transfusions defined as:
        i. A need for at least 6 RBC units in the previous 24 weeks
        ii. No transfusion-free period greater than 35 days in the previous 24 weeks
    e. Reblozyl must be given by a healthcare professional and therefore, will only be covered under the medical benefit
    f. Dosing should be initiated at 1 mg/kg every 3 weeks
        i. If there is no reduction in RBC transfusion burden after 6 weeks of treatment (2 doses) at 1 mg/kg dosing, the dose should be increased to 1.25 mg/kg every 3 weeks
        ii. If there is no reduction in RBC transfusion burden after 9 weeks of treatment (3 doses) at the maximum dose (1.25 mg/kg every 3 weeks), treatment should be discontinued and will not be approved for additional administration
    g. The maximum recommended dose for this indication is 1.25 mg/kg every 3 weeks. Requests for higher doses will not be approved.
    h. Current body weight and requested dosing regimen must be submitted for initial review and each recertification request
    i. Initial approval will be granted for 6 months. Recertification will require documented reduction in RBC transfusion burden after receiving Reblozyl. Approval timeframes after the initial 6 months will be granted as outlined in the approval time frame table in the policy guideline section. **OR**

Anemia in Adults with Myelodysplastic Syndromes

2. Must have a diagnosis of very low-to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
    i. Presence of ring sideroblasts is defined as ≥15% ring sideroblasts or ≥5% ring sideroblasts with an *SF3B1* mutation
    ii. Reblozyl will not be covered for any other subtype myelodysplastic syndrome diagnoses
    b. Must be at least 18 years of age
    c. Must be followed by a hematologist, oncologist, or physician knowledgeable in the treatment of myelodysplastic syndromes
    d. Must have an RBC transfusion burden of ≥2 units/8 week timeframe within preceding 16 weeks
    e. Must be refractory or intolerant to prior erythropoiesis stimulating agent (ESA) containing regimen **OR** be ESA ineligible
        i. Refractory is defined as documentation of non-response **OR** response that is no longer maintained with acceptable ESA-containing regimen defined as:
            1. Recombinant human erythropoietin (Epogen, Procrit or Retacrit) ≥ 40,000 IU/week for at least 8 doses or equivalent **OR**
            2. Darbepoetin alpha (Aranesp) ≥ 500 µg Q3W for at least 4 doses or equivalent

ii. Intolerance requires documentation of discontinuation of prior ESA-containing regimen at any time after introduction due to intolerance or an adverse event
iii. ESA ineligible is defined as a low chance of response to ESA base on endogenous serum erythropoietin level > 200 U/L for subjects not previously treated with ESAs

f. Reblozyl must be given by a healthcare professional and therefore, will only be covered under the medical benefit
g. Dosing should be initiated at 1 mg/kg every 3 weeks
   i. If patient is not RBC transfusion-free after 6 weeks of treatment (2 doses) at 1 mg/kg dosing, the dose should be increased to 1.33 mg/kg every 3 weeks
   ii. If patient is not RBC transfusion-free after 6 weeks of treatment (2 doses) at 1.33 mg/kg dosing, the dose should be increased to 1.75 mg/kg every 3 weeks
   iii. If patient has not had any reduction in RBC transfusion burden after 9 weeks of treatment (3 doses) at 1.75 mg/kg dosing, treatment should be discontinued and will not be approved for additional administration
h. The maximum recommended dose for this indication is 1.75 mg/kg every 3 weeks. Requests for higher doses will not be approved
i. Current body weight and requested dosing regimen must be submitted for initial review and each recertification request
j. Initial approval will be granted for 6 months. Recertification will require documented reduction in RBC transfusion burden after receiving Reblozyl. Approval timeframes after the initial 6 months will be granted as outlined in the approval time frame table in the policy guideline section

HCPCS: J0896

Revcovi-elapegademase-lvlr (Medical & Rx)

1. Prescribed by or in consultation with an immunologist, hematologist/oncologist or a physician that specializes in the treatment of ADA- SCID **AND**
2. The patient has a diagnosis of ADA-SCID confirmed by one of the following (i. or ii)
   i. Absent or very low (< 1% of normal) adenosine deaminase (ADA) catalytic activity in plasma, urine, or dried blood spots prior to the initiation of enzyme replacement therapy **OR**
   ii. Molecular genetic testing confirming bi-allelic mutations in the ADA gene, **AND**
3. Must have elevated deoxyadenosine triphosphate (dATP) levels or total deoxyadenosine (dAdo) nucleotides in erythrocytes (red blood cells) compared to a laboratory standard, **AND**
4. Patient is not a suitable candidate for hematopoietic cell transplantation (HCT) at the time of the request **OR** patient has failed HCT, **AND**
5. Must not have severe thrombocytopenia (considered to be a platelet count of < 50,000 cells/microliter)
6. Revcovi is dosed based on patient weight; therefore, current body weight and requested dose regimen must be submitted for initial review and each recertification request.
7. Revcovi will be reviewed under the **medical benefit** when administered by a health care professional. Revcovi may be self-administered after appropriate training from a healthcare professional and therefore would be considered under the **pharmacy benefit** if self-administered.
8. Initial approval will be for one year
9. Recertification every two years thereafter will require documentation of a positive response to treatment such as one or more of the following:
   a. Improvement in immune status (total lymphocyte and B, T, and natural killer (NK) lymphocyte counts, quantitative immunoglobulin (Ig) concentration [IgG, IgA, IgM])
   b. Improvement in clinical status (infection rate, incidence and duration of hospitalization, and performance status)

c. Normalization of plasma ADA activity, erythrocyte dATP or total dAdo nucleotide levels compared to a laboratory standard

Recommended Dosing:

- The starting dose of Revcovi depends on whether the patient was previously using Adagen. Please refer to the FDA approved prescribing literature for additional dosing and monitoring guidance.
  a. Adagen-naïve patients: the starting weekly dose of Revcovi is 0.4 mg/kg IM based on ideal body weight, divided into two doses (0.2 mg/kg twice weekly), for a minimum of 12 to 24 weeks until immune reconstitution is achieved.
  b. Transitioning from Adagen to Revcovi:
     (1) Previous Adagen weekly dose unknown or dose ≤ 30 U/kg: Revcovi dose minimum of 0.2 mg/kg intramuscularly once weekly
     (2) Previous Adagen weekly dose > 30 U/kg: Calculate Revcovi dose based on the following formula: Revcovi dose (mg/kg) = Adagen dose (U/kg) / 150

Ruzurgi – amifampridine (Rx)

1. Must be prescribed by a neurologist or neuromuscular specialist
2. Must be 6 years of age or older
3. Must have a diagnosis of Lambert-Eaton Myasthenic Syndrome (LEMS) confirmed by electromyography **OR** calcium channel antibody testing
4. Quantity limit 300 tablets per 30 days

Ryplazim- plasminogen, human-tvm (Medical & Rx)

1. Must be prescribed by hematologist, geneticist, pulmonologist, ophthalmologist, or provider specializing in plasminogen deficiency type 1 **AND**
2. Must be 11 months of age or older **AND**
3. Must have diagnosis of plasminogen deficiency type 1 **AND**
4. Must have baseline plasminogen activity level ≤ 45% (Note: if the patient is receiving plasminogen supplementation with fresh frozen plasma, allow for a 7-day washout period before obtaining baseline plasminogen activity level.) **AND**
5. Must have documented history of lesions consistent with a diagnosis of congenital plasminogen deficiency (i.e., ligneous conjunctivitis, ligneous gingivitis, growths in the mucous membrane of the middle ear, respiratory tract, gastrointestinal tract) **AND**
6. If requesting under the pharmacy benefit, provider must attest that the patient/caregiver has received detailed instructions and training and has shown the ability to safely and independently administer Ryplazim.
7. The recommended dosage for Ryplazim is 6.6 mg/kg body weight administered intravenously every 2 to 4 days. Initiate Ryplazim dosing at a frequency of every three days. (See prescribing information for determination of dose and dosing frequency)
8. Quantity Limit: 1 vial/30 days.
   a. Upon each drug review and dose escalation request, the allowed quantity will be reviewed in accordance with the FDA-approved weight-based dosing and, as such, will be limited to the minimum number of vials (rounded up to the nearest whole vial) to obtain the appropriate dose/day supply.
9. Initial approval will be for 12 weeks. Duration of continued approval will be dependent on the patient's initial 12-week response:
   a. For patients who have documented resolution of lesions, approval will be authorized for 12 months.
   b. For patients who do not have resolution of lesions or have new or recurrent lesions, continued approval will be authorized for an additional 12-weeks along with request for additional quantity to optimize dosing frequency. Please note the quantity limit will need to be reviewed.

i. Note: Increase dosing frequency in one-day increments every 4-8 weeks up to every 2 days while reassessing clinical improvement until lesion resolution or until the lesions stabilize without further worsening. If desired clinical change does not occur by 12 weeks, check trough plasminogen activity level.
   1. If the trough plasminogen activity level is ≥ 10% above the baseline trough level, consider other treatment options (i.e., surgical removal of lesions), in addition to plasminogen treatment.
   2. If the trough plasminogen activity level is < 10% above the baseline trough level, repeat plasminogen activity level to confirm. If low plasminogen activity level is confirmed in combination with no clinical efficacy, consider discontinuing plasminogen treatment due to the possibility of neutralizing antibodies.

ii. If patient has a documented clinical efficacy after the additional 12 weeks (i.e., resolution of lesions, improvement in size/number of lesions, trough plasminogen activity level ≥ 10% above baseline trough level), continued approval will be authorized for 12 months.

iii. Ryplazim will not be authorized beyond 24 weeks of therapy if confirmed (repeat) trough plasminogen activity level is <10% above baseline with no clinical efficacy.

Scenesse-afamelanotide (Medical)

Scenesse is indicated to increase pain free light exposure in adult patients with a history of phototoxic reactions from erythropoietic protoporphyria (EPP) and is considered medically necessary when the following criteria have been met (a - i):

a. Must be 18 years of age or older, **AND**
b. Must be prescribed by a physician experienced in the treatment of cutaneous porphyrias such as a dermatologist, hepatologist or geneticist, **AND**
c. Must have a diagnosis of erythropoietic protoporphyria (EPP) confirmed by (i and/or ii)
   i. Biochemical analysis shows abnormally elevated (5-50 times) total erythrocyte protoporphyrin levels in peripheral red blood cells (erythrocytes) compared to the laboratory reference range (e.g., 300-5000 ug/dL; reference range < 80 ug/dL), **AND**
   Erythrocyte fractionation shows a predominance (85% - 100%) of metal-free vs. zinc-chelated protoporphyrin.
   Laboratory report should document total erythrocyte protoporphyrin/porphyrin; erythrocyte zinc protoporphyrin and erythrocyte metal-free (free) protoporphyrin, **OR**
   ii. Molecular genetic testing confirms biallelic pathologic variants in the ferrochelatase (FECH) gene, **AND**
d. Must have a history of documented characteristic symptoms of phototoxicity due to EPP such as burning, itching, swelling, pain and redness of the skin during or after exposure to sunlight or fluorescent light causing reduced quality of life, **AND**
e. Member does not have any of the following conditions:
   - Current Bowen's disease (squamous cell carcinoma in situ), basal cell carcinoma, or squamous cell carcinoma;
   - Personal history of melanoma or dysplastic nevus syndrome;
   - Non-erythropoietic protoporphyria (EPP) skin disorders such as xeroderma pigmentosum, epidermolysis bullosa, polymorphous light eruption (PLE), discoid light eruption (DLE), solar urticaria or due to other porphyrias such as porphyria cutanea tarda and congenital erythropoietic porphyria, **AND**
f. Standard dose is one 16mg implant inserted subcutaneously above the supra-iliac crest every 2 months.
   Administration more frequently than every 2 months (shorter dose interval) will not be covered.

g. A quantity limit of 3 implants per year during periods of high sunlight exposure will apply. Requests for more than 3 implants per year will be evaluated on a case by case basis with provider documentation of medical necessity.
h. Initial approval will be for 6 months.
i. Recertification will require the following:
    - Documentation of a positive response to treatment such as decreased frequency and severity of phototoxic reactions, increased duration of sun exposure, increased quality of life, **AND**
    - Patient has been examined to monitor preexisting and new skin pigmentary lesions
    - Recertification timeframe after the initial approval will be for one year and will be limited to the total number of implants approved for that year. For example: recertification for one year with approval for a maximum of 3 implants to be administered every 2 months during the period of high sunlight exposure.

Additional drug information
Scenesse must be administered by a health care professional proficient in the subcutaneous implantation procedure; therefore, it is covered under the medical benefit.

HCPCS: J7352

Signifor LAR - pasireotide (Medical)

1. Must be prescribed by an endocrinologist **AND**
2. Must have a diagnosis of Cushing's disease
    a. Must not be a candidate for surgery or have had treatment failure with previous surgery. A non-surgical candidate is defined as either having a medical contraindication to surgery or having a tumor which is surgically unapproachable.
    b. A mean free cortisol (mUFC) level will be required at baseline and upon recertification.
    c. Initial approval for Cushing's disease will be for 3 months. Continuation of therapy will require evidence of a reduction in mUFC from baseline. For individuals who achieve a reduction in mUFC after 3 months, recertification will be required every 12 months. **OR**
3. Must have a diagnosis of acromegaly
    a. Must fail to achieve full biochemical control (GH <2.5 ug/L and normal IGF1) on high dose treatment with Sandostatin LAR **OR** Somatuline Depot.
    b. Initial approval for acromegaly will be for 12 months. Recertification for any further approval will require documentation of response to therapy, including:
        i. Reduction or stabilization in tumor volume from baseline assessed by MRI after initial 6 months of therapy **OR**
        ii. Mean growth hormone (GH) less than 2.5 mcg/L and/or a normal insulin-like growth factor- 1 (IGF-1) level after at least 12 months of initial therapy
4. Quantity limit of 1 injection (maximum 60 mg) every 28 days.

HCPCS: J2502

Signifor SC – pasireotide solution (Rx)

1. Must be prescribed by an endocrinologist **AND**
2. Must have a diagnosis of Cushing's disease **AND**
3. Must not be a candidate for surgery or have had treatment failure with previous surgery. A non-surgical candidate is defined as either having a medical contraindication to surgery or having a tumor which is surgically unapproachable.
4. A mean free cortisol (mUFC) level will be required at baseline and upon recertification.
5. Initial approval will be for 3 months. Continuation of therapy will require evidence of a reduction in mUFC from baseline. For individuals who achieve a reduction in mUFC after 3 months, recertification will be required every 12 months.
6. Usual dosage is 0.3 to 0.9mg SC twice a day
7. Quantity limit of 60 doses per 30 days

Soliris - eculizumab (Medical)

1. Must be followed by a neurologist, hematologist, or nephrologist as appropriate for diagnosis **AND**
2. Must have a diagnosis of generalized myasthenia gravis **AND**
   a. Must be at 18 years of age or older
   b. Must be followed by a neurologist. If geographically available, it is also recommended for patients to have been evaluated by a neuromuscular specialist.
   c. Must be anti-acetylcholine receptor (AchR) antibody positive **AND**
   d. Must have had serious side effects or drug failure with pyridostigmine **AND**
   e. Must have had serious side effects or drug failure with at least 1 year of treatment with TWO immunosuppressant agents given alone or in combination such as: prednisone, azathioprine, mycophenolate mofetil, cyclosporine **OR**
   f. Must have had serious side effects or drug failure with at least 1 year of treatment with ONE immunosuppressant agent and, also required chronic plasma exchange or IVIG **AND**
   g. Must have a baseline score of 6 or greater on the Myasthenia Gravis-Activities of Daily Living (MG-ADL) scale.
   h. Initial approval will be for 6 months. Recertification after this initial 6-month period will require documentation of at least a 3-point improvement in the MG-ADL baseline score **AND**
   i. Patients who are currently intubated will be excluded from coverage **OR**
3. Must have a diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) confirmed by a flow cytometry or acid hemolysis test **AND**
   a. Must be prescribed by a hematologist or nephrologist **AND**
   b. For a diagnosis of PNH, must have had serious side effects or drug failure with Ultomiris **OR**
4. Must have a diagnosis of atypical hemolytic uremic syndrome (aHUS) confirmed by ADAMTS13 activity level above 5%.
   a. Patients with Shiga toxin *E. coli* related hemolytic uremic syndrome (STEC-HUS) will be excluded **AND**
   b. Must be prescribed by a hematologist or nephrologist **AND**
   c. For a diagnosis of aHUS, must have had serious side effects or drug failure with Ultomiris **OR**
5. Must have a diagnosis of Neuromyelitis Optica Spectrum Disorder (NMOSD) confirmed by a positive Anti-AQP4 test
   a. Must be at least 18 years of age
   b. Must be prescribed by an ophthalmologist or neurologist
   c. Must have had at least 1 neuromyelitis optica relapse that required rescue therapy (such as corticosteroids or plasma exchange) in the last 12 months
   d. Must have had serious side effects or drug failure of Enspryng and Uplizna

HCPCS: J1300

Somavert - pegvisomant (Rx)

1. Must have a diagnosis of acromegaly
2. Must be prescribed by endocrinologist
3. Patient must have had failure of surgery and/or radiation or is not a candidate for surgery and/or radiation **AND**
4. Patient has had an inadequate response or intolerance to other medical therapies (i.e., cabergoline, bromocriptine, octreotide).
5. IGF-1 levels and liver tests should be monitored and Somavert should be discontinued if LT's are greater than 3 times ULN

Sylvant - siltuximab (Medical)

1. Must be prescribed by an oncologist or hematologist
2. Must have a diagnosis of Multicentric Castleman's disease (MCD) with pathological confirmation on biopsy of involved tissue **AND**
3. Must be human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative
4. Approval will be for 1 year at a time. Further approval will require submission of documentation supporting the absence of disease progression (defined as increase in symptoms, radiologic progression, or deterioration in performance status)

5) Recommended dosage is 11mg/kg given over 1 hour by intravenous infusion every 3 weeks

HCPCS: J2860

Syprine, Clovique, and generic trientine capsules (Rx)

1. Must have a diagnosis of Wilson's Disease
2. Must have had serious side effects or drug failure with penicillamine tablets (the generic for Depen)
3. Quantity limit of 240 per 30 days

Tavneos- avacopan (Rx)

1. Must be 18 years of age or older **AND**
2. Must be prescribed by or in consultation with a rheumatologist, nephrologist, pulmonologist, or immunologist **AND**
3. Must have a diagnosis of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] or microscopic polyangiitis [MPA]) **AND**
4. Provider must attest that the patient has active and severe disease
    a. Active disease is defined as new, persistent, or worsening clinical signs and/or symptoms attributed to GPA or MPA and not related to prior damage
    b. Severe disease is defined as vasculitis with life- or organ-threatening manifestations (i.e., alveolar hemorrhage, glomerulonephritis, central nervous system vasculitis, mononeuritis multiplex, cardiac involvement, mesenteric ischemia, limb/digit ischemia) **AND**
5. Must have a positive test for antibodies to either proteinase 3 (PR3) or myeloperoxidase (MPO)
    a. If patient tests negative for PR3 or MPO antibodies, then histological evidence of GPA or MPA via biopsy will be acceptable **AND**
6. Tavneos must be used as adjunctive treatment in combination with standard of care therapy (i.e., cyclophosphamide, azathioprine, mycophenolate mofetil, rituximab, glucocorticoids) **AND**
7. Must have an estimated glomerular filtration rate (eGFR) $\geq$ 15 mL/min/1.73m^2 **AND**
8. Tavneos will not be approved for Eosinophilic Granulomatosis with Polyangiitis (EGPA)
9. Initial approval will be for 6 months. Recertification will require documentation of disease remission, defined as the absence of clinical signs or symptoms attributed to GPA or MPA while on Tavneos. Recertification requires that Tavneos will be used in combination with standard of care therapy. Recertifications will be approved for 2 years. Given the heterogenous nature of this disease that may

have multi-organ involvement, consideration may be given on recertification from provider showing clear improvement in symptoms attributed to the use of Tavneos which warrants continued use (such as reduced rate of relapse, corticosteroid dose reduction, improvement in eGFR and albuminuria)
10. Quantity limit: 180 capsules/30 days.

Tepezza –teprotumumab-trbw (Medical)

1. Member must be at least 18 years old
2. Must be prescribed by an endocrinologist or ophthalmologist
3. Must have a diagnosis of Graves' disease with active thyroid eye disease (TED)
4. Must have a score of at least 4 on the Clinical Activity Score (CAS)
5. Prescriber must attest that the member's thyroid level has been normalized before beginning treatment
6. FDA approved dosing is 10 mg/kg for the first infusion, followed by 20 mg/kg every 3 weeks for 7 additional infusions
7. Approval will be for 24 weeks to allow for 8 infusions total
8. Retreatment will not be covered as there is no published literature available to support the use of Tepezza in patients who have already received a 24-week treatment
9. The CAS Score includes the following elements (Note: a 7-point scale excluding the last three elements (h-j) is used when no previous assessment is available):
    a. Spontaneous retrobulbar pain
    b. Pain on eye movements
    c. Eyelid erythema
    d. Conjunctival injection
    e. Chemosis
    f. Swelling of the caruncle
    g. Eyelid edema or fullness
    h. Increase in proptosis $\geq$ 2 mm
    i. Decreased eye movements $\geq$ 5º any direction
    j. Decreased visual acuity $\geq$ 1 line of Snellen chart

HCPCS: J3241

Ultomiris – ravulizumab-cwvz injection (Medical)

1. Must be one month of age or older **AND**
2. Must have a diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) confirmed by a flow cytometry or acid hemolysis test **AND**
    a. Must be prescribed by a hematologist
2. Must have a diagnosis of atypical hemolytic uremic syndrome (aHUS) confirmed by ADAMTS13 activity level above 5%
    a. Patients with Shiga toxin *E. coli* related hemolytic uremic syndrome (STEC-HUS) will be excluded **AND**
3. Must be prescribed by a hematologist or nephrologist
4. All other non-FDA approved indications will be excluded from coverage

HCPCS: J1303

Uplizna – inebilizumab-cdon (Medical)

1. Must have a diagnosis of Neuromyelitis Optica Spectrum Disorder (NMOSD) confirmed by a positive anti-aquaphorin-4 (AQP4) antibody test
2. Must be at least 18 years of age
3. Must be prescribed by an ophthalmologist or neurologist
4. Must have had at least 1 neuromyelitis optica relapse that required rescue therapy (such as corticosteroids or plasma exchange) in the last 12 months

5. Must have had serious side effects or drug failure with Enspryng

Zokinvy-lonafarnib (Rx)

1. Must be prescribed by or in consultation with a physician knowledgeable in the management of Hutchinson-Gilford Progeria Syndrome and processing-deficient Progeroid Laminopathies
2. Must have a diagnosis of one of the following:
    a. Hutchinson-Gilford progeria syndrome (HGPS) (must meet both i and ii)
        i. Presence of clinical features (e.g., growth deficiency, characteristic facial features, ectodermal, musculoskeletal) **AND**
        ii. Heterozygous variant in LMNA gene confirmed by genetic testing
        <u>*Note*</u>: Individuals with classic genotype HGPS (~90% individuals with HGPS) are heterozygous for pathogenic variant c.1824C>T. Individuals with nonclassic genotype HGPS (~10% individuals with HGPS) are heterozygous for another *LMNA* pathogenic variant in exon 11 splice junction or intron 11 that results in production of progerin. **OR**
    b. Processing-deficient progeroid laminopathy with either:
        i. Heterozygous *LMNA* mutation with progerin-like protein accumulation
        ii. Homozygous or compound heterozygous *ZMPSTE24* mutations
3. Patient must be 12 months of age or older
4. Patient must have a BSA of 0.39 m^2 or greater
5. Requested dose is appropriate for patient's BSA (see table 1 and 2 for FDA-approved dosing)
6. Provider attestation indicating that the patient does not have overt renal, hepatic, or pulmonary disease or immune dysfunction
7. Zokinvy will not be approved for other Progeroid Syndromes or processing-proficient Progeroid Laminopathies
8. Quantity limit of 30 capsules per 30 days.
    a. Upon each drug review and dose escalation request, the allowed quantity will be reviewed in accordance with FDA-approved BSA-based dosing (see table 1 and 2) and, as such, will be limited to minimum number of capsules of each strength to obtain the appropriate daily dose. For example, a patient with a BSA of 0.71 to 0.81 receiving a dose of 115mg/m^2 twice daily, will require a total daily dose of 175 mg. To obtain a daily dose of 175 mg, the patient would need 2-50 mg capsules/day (60 capsules/30 days) and 1-75 mg capsule/day (30 capsules/30 days).
9. Initial authorization period: 4 months. Subsequent recertifications after the initial 4-month approval will require documentation that patient is tolerating therapy, provider attestation that patient is responding to therapy, and is on appropriate dose for BSA.
10. *Please note:* for applicable lines of businesses (Commercial, Exchange, Child Health Plus), a split-fill program will apply to new starts only. An override to bypass the split-fill program will be provided for existing users that have been maintained on Zokinvy.

Table 1 and Table 2: FDA-approved dosing for Zokinvy

Table 1 provides the BSA-based dosage recommendations for the starting dosage of 115 mg/m² twice daily.

Table 1: Recommended Dosage and Administration for 115 mg/m² Body Surface Area-Based Dosing

BSA (m²)	Total Daily Dosage Rounded to Nearest 25 mg	Morning Dosing Number of Capsule(s)		Evening Dosing Number of Capsule(s)	
		ZOKINVY 50 mg	ZOKINVY 75 mg	ZOKINVY 50 mg	ZOKINVY 75 mg
0.39 - 0.48	100	1		1	
0.49 - 0.59	125		1	1	
0.6 - 0.7	150		1		1
0.71 - 0.81	175	2			1
0.82 - 0.92	200	2		2	
0.93 - 1	225	1	1	2	

Table 2 provides the BSA-based dosage recommendations for the dosage of 150 mg/m² twice daily.

Table 2: Recommended Dosage and Administration for 150 mg/m² Body Surface Area-Based Dosing

BSA (m²)	Total Daily Dosage Rounded to Nearest 25 mg	Morning Dosing Number of Capsule(s)		Evening Dosing Number of Capsule(s)	
		ZOKINVY 50 mg	ZOKINVY 75 mg	ZOKINVY 50 mg	ZOKINVY 75 mg
0.39 - 0.45	125		1	1	
0.46 - 0.54	150		1		1
0.55 - 0.62	175	2			1
0.63 - 0.7	200	2		2	
0.71 - 0.79	225	1	1	2	
0.8 - 0.87	250	1	1	1	1
0.88 - 0.95	275		2	1	1
0.96 - 1	300		2		2

Figure 1a - Isturisa Efficient Dosing Chart

This chart reflects the number of tablets of each strength that will be covered to make any given dose of Isturisa within the FDA approved limit.

Dose	**1 mg**	**5 mg**	**10 mg**
2 mg BID	120 tablets/30 days		
3 mg BID	180/30		
4 mg BID	240/30		
5 mg BID		60/30	
6 mg BID	60/30	60/30	
7 mg BID	120/30	60/30	
8 mg BID	180/30	60/30	
9 mg BID	240/30	60/30	
10 mg BID			60/30
11 mg BID	60/30		60/30
12 mg BID	120/30		60/30
13 mg BID	180/30		60/30
14 mg BID	240/30		60/30
15 mg BID		60/30	60/30
16 mg BID	60/30	60/30	60/30
17 mg BID	120/30	60/30	60/30

18 mg BID	180/30	60/30	60/30
19 mg BID	240/30	60/30	60/30
20 mg BID			120/30
21 mg BID	60/30		120/30
22 mg BID	120/30		120/30
23 mg BID	180/30		120/30
24 mg BID	240/30		120/30
25 mg BID		60/30	120/30
26 mg BID	60/30	60/30	120/30
27 mg BID	120/30	60/30	120/30
28 mg BID	180/30	60/30	120/30
29 mg BID	240/30	60/30	120/30
30 mg BID			180/30

CODES:
Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.
Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

Approval Time Periods – Initial and Recertification Reviews:

1. Unless otherwise stated within the individual drug criteria, approval time periods are listed in the table below
2. Continued approval at time of recertification will require documentation that the drug is providing ongoing benefit to the patient in terms of improvement or stability in disease state or condition. Such documentation may include progress notes, imaging or laboratory findings, and other objective or subjective measures of benefit which support that continued use of the requested product is medically necessary. Also, ongoing use of the requested product must continue to reflect the current policy's preferred formulary [Recertification reviews may result in the requirement to try more cost-effective treatment alternatives as they become available (i.e., generics or other guideline-supported treatment options)] and the requested dose must continue to meet FDA approved or off-label/guideline supported dosing

Line of Business	Rx Initial approval	Rx Continued approval	Medical Initial approval	Medical Recert
SafetyNet (Medicaid, HARP, CHP, Essential Plan)	1 year (or as stated within individual drug policy)	2 years (or as stated within individual drug policy)	Outpatient Hospital – 6 months	Outpatient Hospital – 6 months
			Home Care or Office Based – 2 years	Home Care or Office Based – 2 years
Commercial / Exchange	1 year (or as stated within individual drug policy)	2 years (or as stated within individual drug policy)	Outpatient Hospital – 6 months	Outpatient Hospital – 6 months
			Home Care or Office Based – 2 years	Home Care or Office Based – 2 years
Medicare	Defined in Medicare Drug Policy	Defined in Medicare Drug Policy	Outpatient Hospital – 2 years	Outpatient Hospital – 6 months
			Home Care or Office Based – 2 years	Home Care or Office Based – 2 years

POLICY GUIDELINES:

1. Prior authorization is contract dependent.
2. This policy is applicable to drugs that are included on a specific drug formulary (RX benefit only). If a drug referenced in this policy is non-formulary, please reference the Non-Formulary Medication Exception Review Policy for review guidelines.
3. Supportive documentation of previous drug use must be submitted for any criterion that requires the trial of a preferred agent if the preferred drug is not found in claims history.
4. Dose and frequency should be in accordance with the FDA label or recognized compendia (for off-label uses). When services are performed in excess of established parameters, they may be subject to review for medical necessity.
5. For contracts where Insurance Law § 4903(c-1), and Public Health Law § 4903(3-a) are applicable, if trial of preferred drug(s) is the only criterion that is not met for a given condition, and one of the following circumstances can be substantiated by the requesting provider, then trial of the preferred drug(s) will not be required. The provider must make their intent to override a trial of the preferred drugs clear and must provide rationale and supporting documentation for one of the following:
    - The required prescription drug(s) is (are) contraindicated or will likely cause an adverse reaction or physical or mental harm to the member;
    - The required prescription drug is expected to be ineffective based on the known clinical history and conditions and concurrent drug regimen;
    - The required prescription drug(s) was (were) previously tried while under the current or a previous health plan, or another prescription drug or drugs in the same pharmacologic class or with the same mechanism of action was (were) previously tried and such prescription drug(s) was (were) discontinued due to lack of efficacy or effectiveness, diminished effect, or an adverse event;
    - The required prescription drug(s) is (are) not in the patient's best interest because it will likely cause a significant barrier to adherence to or compliance with the plan of care, will likely worsen a comorbid condition, or will likely decrease the ability to achieve or maintain reasonable functional ability in performing daily activities;
    - The individual is stable on the requested prescription drug. The medical profile of the individual (age, disease state, comorbidities), along with the rational for deeming stability as it relates to standard medical practice and evidence-based practice protocols for the disease state will be taken into consideration.
    - The above criteria are not applicable to requests for brand name medications that have an AB rated generic. We can require a trial of an AB-rated generic equivalent prior to providing coverage for the equivalent brand name prescription drug.
6. This policy is subject to frequent revisions as new medications come onto the market. Some drugs will require prior authorization prior to criteria being added to the policy.

UPDATES:

Date:	Revision:
12/21	Revised
11/21	Revised
10/21	Revised
9/21	Revised
8/21	Revised
7/21	Revised
6/21	Revised
5/21	Revised
5/21	P&T Committee Approval
4/21	Revised
3/21	Revised
2/21	Revised
1/21	Created

REFERENCES:

In addition to the full FDA approved prescribing information for each individual drug, the following references have been utilized in creating this policy and specific drug criteria:

Aldurazyme-

1. Panel VPBMSHCGatMA. Laronidase (Aldurazyme): National PBM Drug Monographs; 2004

Arcalyst-

1. Adler Y, Charron P, Imazio M, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases. European Heart Journal. 2015;36(42):2921-2964.

Bylvay-

1. Amirneni S, Haep N, Gad MA, et al. Molecular overview of progressive familial intrahepatic cholestasis. World J Gastroenterol. 2020 Dec 21;26(47):7470-7484.

Evkeeza-

1. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;139:e1082-e1143.

Increlex –

1. Guevara-Aguirre J, et al, "A randomized, double blind, placebo-controlled trial on safety and efficacy of recombinant human insulin-like growth factor-1 in children with growth hormone receptor deficiency", Journal of Clinical Endocrinology & Metabolism, 1995;80:1393-8
2. Backeljauw PF, et al, "Therapy for 6.5-7.5years with recombinant insulin-like growth factor 1 in children with growth hormone insensitivity syndrome: A clinical research center study.", Journal of Clinical Endocrinology & Metabolism, 2001;86:1504-10

Reblozyl-

1. Celgene Corporation Package Insert for Reblozyl. April 2020.

Somavert –

1. Ezzat S. Pharmacological approach to the treatment of acromegaly. Neurosurgery Focus. 2004; 14(4): E3.

Tavneos-

1. Bossuyt, X., Cohen Tervaert, JW., Arimura, Y. *et al.* Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. *Nat Rev Rheumatol* **13,** 683–692 (2017). https://doi.org/10.1038/nrrheum.2017.140

2. Chung SA, Langford CA, Maz M, et al. 2021 American College of Rheumatology/Vasculitis Foundation guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheumatol. 2021 Aug;73(8):1366- 1383.

Zokinvy-

1. Rare Diseases FAQ. Available at: https://www.genome.gov/FAQ/Rare-Diseases. Accessed January 15, 2021
2. Zokinvy™. Package insert. Eiger Biopharmaceuticals;2020.
3. Gordon LB, Brown WT, Collins FS. Hutchinson-Gilford Progeria Syndrome. 2003 Dec 12 [Updated 2019 Jan 17]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available at https://www.ncbi.nlm.nih.gov/books/NBK1121/. Accessed on January 15, 2020.
4. Gordon LB, Shappell H, Massaro J, et al. Association of lonafarnib treatment vs. no treatment with mortality rate in patients with Hutchinson-Gilford Progeria Syndrome. *JAMA*. 2018;319(16):1687-1695.
5. Gordon LB, Kleinman ME, Miller DT, et al. Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson-Gilford Progeria Syndrome. *Proc Natl Acad Sci USA*. 2012;109(41):16666-16671.
6. Gordon LB, Kleinman ME, Massaro J, et al. Clinical trial of the protein farnesylation inhibitors lonafarnib, pravastatin, and zoledronic acid in children with Hutchinson-Gilford Progeria Syndrome. *Circulation*. 2016;134(2):114-125.

Reference number(s)
C21508-A

HARVARD PILGRIM MEDICAL POLICY

RYPLAZIM (plasminogen, human-tvmh)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Ryplazim is plasma-derived human plasminogen indicated for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia).

All other indications are considered experimental/investigational and not medically necessary.

II. DOCUMENTATION

Submission of the following information is necessary to initiate the prior authorization review:
A. Initial Requests: Medical records (e.g., chart notes, lab reports) documenting a baseline plasminogen activity level and a history of lesions and symptoms consistent with diagnosis.
B. Continuation Requests: Medical records (e.g., chart notes, lab reports) documenting disease stability or improvement.

III. CRITERIA FOR INITIAL APPROVAL

Plasminogen deficiency type 1 (hypoplasminogenemia)
Authorization of 12 months may be granted for treatment of plasminogen deficiency type 1 (hypoplasminogenemia) when all of the following criteria are met:
A. Member has a baseline plasminogen activity level of 45% or less at baseline.
B. Member has a documented history of lesions and symptoms consistent with a diagnosis of plasminogen deficiency type 1 (e.g., ligneous conjunctivitis, ligneous gingivitis or gingival overgrowth, vision abnormalities, respiratory distress and/or obstruction, abnormal wound healing).

IV. CONTINUATION OF THERAPY

Authorization of 12 months may be granted for members with an indication listed in Section III who are experiencing benefit from therapy as evidenced by disease stability or disease improvement (e.g., improvement in lesion number and/or size, absence of new lesion development, improvement in respiratory function, increased quality of life).

V. QUANTITY LIMIT

Coverage will be limited to the FDA-approved dosing regimen. Dosage and frequency of approved off-label uses shall not exceed the approved, requested dose or up to the maximum FDA-approved dosing regimen.

Indication	FDA- approved loading dose (if applicable)	FDA-approved maximum maintenance dose and frequency
Plasminogen deficiency type 1	N/A	6.6 mg/kg IV once every 2 days

VI. REFERENCES

1. Ryplazim [package insert]. Laval, Quebec, Canada: Prometic Bioproduction Inc; June 2021.
2. Shapiro AD, Nakar C, Parker JM, et al. Plasminogen replacement therapy for the treatment of children and adults with congenital plasminogen deficiency. *Blood*. 2018;131(12):1301-1310.
3. Celkan T. Plasminogen deficiency. J Thromb Thrombolysis. January, 2017; 43(1):132-138.

Nov. 2, 2021

HIGHMARK HEALTH OPTIONS

PROVIDER NOTICE

Effective Jan. 1, 2022

Prior Authorization Required for Saphnelo, Nexviazyme, Flolan/Veletri, Empaveli, Ryplazim, and Uptravi

As a continued effort to improve the quality of care for our members, Highmark Health Options reminds providers about the prior authorization process for the medications listed on the following pages. Failure to obtain authorization will result in a claim denial.

The prior authorization process applies to all Highmark Health Options members. Medical necessity criteria for the medications listed below is outlined in the medication policies section of the Highmark Health Options website. Scan the QR code or visit https://hho.fyi/meds.

Procedure Codes Requiring Authorization

DRUG NAME	HCPCS
anifrolumab-fnia (Saphnelo)	J3590*
avalglucosidase alfa-ngpt (Nexviazyme)	J3590*
epoprostenol (Flolan; Veletri)	J1325
pegcetacoplan (Empaveli)	J7799*
plasminogen, human-tvmh (Ryplazim)	J3590*
selexipag IV (Uptravi)	J3490*

*These medications will be reviewed under the applicable miscellaneous procedure code until a permanent code is assigned.

Any decision to deny a prior authorization or to authorize a service is made by a licensed pharmacist based on:

- Characteristics of the local delivery system.
- Established clinical criteria.
- Individual member needs.

Authorization does not guarantee payment of claims. Any medication listed above will be reimbursed by us only if it is:

- Medically necessary.
- A covered service.
- Provided to an eligible member.

If you have questions regarding the authorization process or how to submit authorizations, please contact Highmark Health Options Pharmacy Services at 1-844-325-6251, Monday–Friday, 8 a.m.–5 p.m.

Reminder: Changes to Authorization Requests

While the new provider portal is being developed, temporary manual processes will be in place for:

- Medication authorizations (medical benefit J codes). Submit by fax to 1-855-476-4158 or call the Pharmacy Department at 1-844-325-6251 Monday–Friday, 8 a.m.–5 p.m.
- All other authorizations. Submit authorizations by calling Utilization Management at 1-844-325-6251, Monday–Friday, 8 a.m.–5 p.m.

During the transition to the new provider portal, you can continue to use NaviNet for eligibility inquiry, claims inquiry, updates, and more. The temporary manual process will be in place until new online tools are available.

Highmark Health Options is available to:

- Answer your calls, receive incoming faxes, and build the authorization shells.
- Provide an automatic approval authorization without a clinical review in accordance with established guidelines, in some instances.
- Update you on your appeals and claims disputes submissions.

If you have questions or concerns, contact Provider Services at 1-844-325-6251.

Ryplazim® (plasminogen, human-tvmh)
(Intravenous)

Document Number: IC-0611

Last Review Date: 07/01/2021
Date of Origin: 07/01/2021
Dates Reviewed: 07/2021

I. Length of Authorization

Coverage will be provided initially for 12 weeks.

- In patients with complete response, coverage will be renewed annually thereafter.
- In patients with less than complete response, coverage will be renewed for an additional 12 weeks to optimize frequency of administration.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Ryplazim 68.8 mg single-dose vial: 11 vials per 2 days

B. Max Units (per dose and over time) [HCPCS Unit]:

- 757 mg (11 vials) every 2 days

III. Initial Approval Criteria [1,2]

Coverage is provided in the following conditions:

- Patient is at least 11 months of age; **AND**
- Patient blood pressure is controlled prior to initiation of treatment; **AND**
- Patient has healing of lesions or wounds suspected as a source of a recent bleeding event prior to initiating therapy; **AND**
- Patient has had a baseline plasminogen activity measured prior to therapy and plasminogen activity level is ≤ 45% *(Note: If patient is receiving plasminogen supplementation with fresh frozen plasma, allow for a 7-day washout period before obtaining baseline plasminogen activity level)*; **AND**

Universal Criteria [1]

- Patients on concomitant therapy with anticoagulants, antiplatelet drugs, or other agents which may interfere with normal coagulation will be monitored during and for 4 hours after infusion of Ryplazim; **AND**

Plasminogen Deficiency Type 1 (Hypoplasminogenemia) † Φ

- Patient has a history of visible or non-visible lesions (e.g., confirmed by computed tomography, magnetic resonance imaging, ultrasound, etc.)

Note: All patients must initiate therapy at a frequency of every three days.

† FDA-approved indication(s); Φ Orphan Drug

IV. Renewal Criteria [1]

Coverage can be renewed based on the following criteria:

- Patient continues to meet indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe bleeding, respiratory distress, anaphylaxis and severe allergic reactions, etc.; **AND**
  - Patient has demonstrated a beneficial response to therapy (i.e., resolution of lesions); **OR**
  - Patient's lesions have not resolved after an initial 12 weeks of therapy OR there are new or recurrent lesions; **AND**
    - Patient may increase dosage frequency, as outlined below, in one day increments every 4-8 weeks up to the max dosing frequency (i.e., every two days); **AND**
    - Re-assess trough plasminogen activity level if, after 12 additional weeks of dose optimization, no clinical effect has been noted; **AND**
      - If trough plasminogen activity level is <10% above baseline, repeat trough. If low plasminogen is confirmed AND no clinical effect has been demonstrated, consider treatment discontinuation

V. Dosage/Administration[1]

Indication	Dose
Type 1 Hypo-plasminogenemia	The recommended dosage of Ryplazim is 6.6 mg/kg of body weight administered intravenously every 2 to 4 days. Initiate dosing at a frequency of every three days, then adjust as below. Determination of Dosing Frequency • Obtain baseline plasminogen activity level (allow for a 7-day washout period if the patient has been receiving fresh frozen plasma); **AND** • Obtain trough plasminogen activity level 72 hours following the initial dose and prior to the second dose; **AND** – Plasminogen activity level is <10% above baseline, increase frequency of therapy to every 2 days

	– Plasminogen activity level is ≥10 and ≤20% above baseline, maintain therapy at frequency of every 3 days – Plasminogen activity level is >20% above baseline, decrease frequency of therapy to every 4 days • Maintain dosing frequency above for 12 weeks while treating active lesions; **AND** – If lesions have resolved, continue therapy and re-assess in 12 weeks – If lesions have not resolved, or there are new or recurrent lesions, increase the dosing frequency in one-day increments every 4-8 week up to dosing every 2 days. If desired clinical effect is not seen in 12 weeks, assess trough plasminogen activity level; **AND** o Plasminogen activity level ≥10% above baseline, consider other additional treatments (e.g., surgical removal) o Plasminogen activity level <10% above baseline, then repeat trough to confirm. If low trough is confirmed, consider discontinuing therapy if no clinical efficacy has been demonstrated
Plasminogen activity (%) as absolute change	

VI. Billing Code/Availability Information

HCPCS Code:
- J3590 – Unclassified biologics

NDC:
- Ryplazim 68.8 mg single-dose vial: 70573-0099-xx

VII. References

1. Ryplazim [package insert]. Laval, Quebec, CA; Prometric Bioproduction, Inc.; June 2021. Accessed June 2021.
2. Shapiro AD, Nakar C, Parker JM,. Plasminogen replacement therapy for the treatment of children and adults with congenital plasminogen deficiency. Blood. 2018 Mar 22;131(12):1301-1310. doi: 10.1182/blood-2017-09-806729. Epub 2018 Jan 10..

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
E88.02	Plasminogen deficiency

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Clinical Criteria

Subject:	Ryplazim (plasminogen, human-tvmh)		
Document #:	ING-CC-0203	**Publish Date:**	09/01/2021
Status:	New	**Last Review Date:**	08/20/2021

Table of Contents

Overview

This document addresses the use of Ryplazim (plasminogen, human-tvmh), an intravenously administered human plasma-derived plasminogen product that is FDA approved for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia).

Plasminogen deficiency (PLGD) type 1, or hypoplasminogenemia, is an ultra-rare genetic disorder caused by alterations in the PLG gene resulting in reduced plasminogen levels. Individuals with PLGD type 2 have normal plasminogen levels with reduced activity, and often have no symptoms. Hypoplasminogenemia may be diagnosed by molecular genetic testing which is available only at specialized laboratories. It is often identified through characteristic symptoms, family and patient history, and lab tests measuring the activity of plasminogen. Reduced plasminogen activity results in excess fibrin which builds up in mucous membranes to form thick growths or lesions. These occur most often in the conjunctiva (ligneous conjunctivitis), but may be present in mouth, nose, ear, gastrointestinal tract, respiratory tract, and genitourinary track, causing significant morbidity. Though plasminogen plays a role in clot formation and breakdown, evidence does not suggest an increased risk for thrombosis in individuals with PLGD type 1. Prior to the approval of Ryplazim, treatment options were limited to surgery and non-specific therapies showing inconsistent success.

Ryplazim was studied in a small single-arm phase 2/3 study which enrolled individuals with a documented history of lesions and symptoms consistent with a diagnosis of plasminogen deficiency type 1 and a plasminogen activity level ≤45%. Ryplazim treatment for 12 weeks showed an improvement in plasminogen activity levels and an improvement in the number/size of lesions or organ function. It is administered as an intravenous infusion every 2 to 4 days. Plasminogen activity and active lesions should be assessed at baseline and monitored throughout treatment to guide dosing frequency. If the desire clinical change does not occur by 12 weeks, plasminogen activity is checked. Other treatment options, such as surgery, may be added to plasminogen treatment if plasminogen activity is ≥10% above initial baseline level. If low plasminogen activity level (<10% [absolute change] above baseline trough level) is confirmed in combination with no clinical efficacy, consider discontinuing treatment due to possibility of neutralizing antibodies.

Similar to other products derived from human plasma, such as IV immunoglobulin products, Ryplazim carries a remote risk of transmitting infectious agents or viruses. However, risk is mitigated based on donor screening and manufacturing processes. Ryplazim also has a warning for tissue sloughing which may occur at mucosal lesions as plasminogen activity is restored. Based on its mechanism of action patients should also be monitored for bleeding, neutralizing antibody formation, and laboratory abnormalities such as elevated levels of D-dimer.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Ryplazim (plasminogen, human-tvmh)

Initial requests for Ryplazim (plasminogen, human-tvmh) may be approved if the following criteria are met:

I. Individual has a diagnosis of plasminogen deficiency type 1 (hypoplasminogenemia); **AND**
II. The diagnosis has been confirmed by the following (Shapiro 2018):
    a. Individual has a plasminogen activity level ≤ 45%; **AND**
    b. Individual has a history of lesions and symptoms consistent with a diagnosis of congenital plasminogen deficiency.

Continuation requests for Ryplazim (plasminogen, human-tvmh) may be approved if the following criteria are met:

I. There is confirmation of clinically significant response to therapy as evidenced by the following:
   A. Resolution or improvement of baseline lesions (if present) with no new or recurrent lesions; **OR**
   B. Individual had achieved or maintained trough plasminogen activity level ≥10% above initial baseline level.

Requests for Ryplazim (plasminogen, human-tvmh) may not be approved for the following:

I. All indications not included above; **OR**
II. Individual with plasminogen deficiency type 2.

Initial Approval Duration: 12 weeks
Continuation Approval Duration: 1 year

Coding

The following codes for treatments and procedures applicable to this document 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 policy. 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

J3450	Unclassified drugs (when specified at (plasminogen, human-tvmh) [Ryplazim]
J3590	Unclassified biologics (when specified at (plasminogen, human-tvmh) [Ryplazim]

ICD-10 Diagnosis

All diagnoses pend

Document History

New: 08/20/2021
Document History:

- 08/20/2021 – Annual Review: Add new criteria clinical criteria for Ryplazim. Coding Reviewed: Added HCPCS J3490, J3590. All diagnoses pend.

References

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2021. URL: http://www.clinicalpharmacology.com. Updated periodically.
2. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: July 12, 2021.
3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2021; Updated periodically.
5. Shapiro AD, Nakar C, Parker JM, et al. Plasminogen replacement therapy for the treatment of children and adults with congenital plasminogen deficiency. Blood. 2018 Mar 22;131(12):1301-1310. doi: 10.1182/blood-2017-09-806729.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

Reference number(s)
4781-A

SPECIALTY GUIDELINE MANAGEMENT

RYPLAZIM (plasminogen, human-tvmh)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Ryplazim is plasma-derived human plasminogen indicated for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia).

All other indications are considered experimental/investigational and not medically necessary.

II. DOCUMENTATION

Submission of the following information is necessary to initiate the prior authorization review:
A. Initial Requests: Medical records (e.g., chart notes, lab reports) documenting a baseline plasminogen activity level and a history of lesions and symptoms consistent with diagnosis.
B. Continuation Requests: Medical records (e.g., chart notes, lab reports) documenting disease stability or improvement.

III. CRITERIA FOR INITIAL APPROVAL

Plasminogen deficiency type 1 (hypoplasminogenemia)
Authorization of 12 months may be granted for treatment of plasminogen deficiency type 1 (hypoplasminogenemia) when all of the following criteria are met:
A. Member has a baseline plasminogen activity level of 45% or less at baseline.
B. Member has a documented history of lesions and symptoms consistent with a diagnosis of plasminogen deficiency type 1 (e.g., ligneous conjunctivitis, ligneous gingivitis or gingival overgrowth, vision abnormalities, respiratory distress and/or obstruction, abnormal wound healing).

IV. CONTINUATION OF THERAPY

Authorization of 12 months may be granted for members with an indication listed in Section III who are experiencing benefit from therapy as evidenced by disease stability or disease improvement (e.g., improvement in lesion number and/or size, absence of new lesion development, improvement in respiratory function, increased quality of life).

V. REFERENCES

1. Ryplazim [package insert]. Laval, Quebec, Canada: Prometic Bioproduction Inc; June 2021.

2. Shapiro AD, Nakar C, Parker JM, et al. Plasminogen replacement therapy for the treatment of children and adults with congenital plasminogen deficiency. *Blood*. 2018;131(12):1301-1310.
3. Celkan T. Plasminogen deficiency. J Thromb Thrombolysis. January, 2017; 43(1):132-138.

Drug Therapy Guidelines	Applicable*	Ryplazim® (plasminogen, human-tvmh)
Medical Benefit	x	**Effective:** 11/29/21
Pharmacy- Formulary 1		**Next Review:** 09/22
Pharmacy- Formulary 2		**Date of Origin**: 09/21
Pharmacy- Formulary 3/Exclusive		**Review Dates:** 09/21
Pharmacy- Formulary 4/AON		

I. Medication Description

Ryplazim is made from purified human plasma and works to increase the level of plasminogen in the blood to temporarily correct the plasminogen deficiency and reduce or resolve lesions.

II. Position Statement

Coverage is determined through a prior authorization process with supporting clinical documentation for every request.

III. Policy

Coverage of Ryplazim is available when the following criteria have been met:

- The medication is prescribed by or consultation with a hematologist, pulmonologist, ophthalmologist or geneticist **AND**
- Member has a diagnosis of plasminogen deficiency type 1 confirmed by BOTH of the following:
  - History of hypoplasminogenemia with a plasminogen activity level ≤ 45% **AND**
  - Documented history of lesions and symptoms consistent with a diagnosis of congenital plasminogen deficiency

IV. Quantity Limitations

Coverage is available to allow for sufficient quantities for weight-based dosing (in accordance with FDA approved prescribing information).

V. Coverage Duration

Coverage is available for 12 weeks and may be renewed.

VI. Coverage Renewal Criteria

Coverage can be renewed in 6 month increments based upon the following criteria:

- The prescriber attests that the member has experienced a reduction of external and/or internal lesions.

VII. Billing/Coding Information

Ryplazim is available as 50mL vials that contain 5.5mg/mL of plasminogen after reconstitution.

VIII. Summary of Policy Changes

- 11/29/21: new policy

IX. References

1. Ryplazim (plasminogen) [package insert]. Des Prairies Laval, Quebec: Prometic; Jun 2021.
2. National Center for Advancing Translational Sciences. Type 1 plasminogen deficiency. Available at: https://rarediseases.info.nih.gov/diseases/4380/type-1-plasminogen-deficiency#ref_13158. Accessed August 24, 2021.
3. Rare Coagulation Disorders. Plasminogen Deficiency. Available at http://www.rarecoagulationdisorders.org/diseases/plasminogen-deficiency/treatments-and-medications. Accessed August 24, 2021.
4. Medline Plus. Congenital plasminogen deficiency. Available at: https://medlineplus.gov/genetics/condition/congenital-plasminogen-deficiency/#references. Accessed August 24, 2021.
5. Commissioner of the FDA Approves First Treatment for Patients with Plasminogen Deficiency, a Rare Genetic Disorder. U.S. Food and Drug Administration. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-patients-plasminogen-deficiency-rare-genetic-disorder. Accessed August 24, 2021.

**These guidelines are not applicable to benefits covered under Medicare Advantage. Medicare Advantage benefit coverage requests are reviewed in accordance with the guidance set forth in Chapter 15 Section 50 of the Centers for Medicare & Medicaid Services Medicare Benefit Policy Manual.*

The Plan fully expects that only appropriate and medically necessary services will be rendered. The Plan reserves the right to conduct pre-payment and post-payment reviews to assess the medical appropriateness of the above-referenced therapies.

The preceding policy is a guideline to allow for coverage of the pertinent medication/product, and is not meant to serve as a clinical practice guideline.

Ryplazim® (Plasminogen, Human-Tvmh)

Policy Number: 2022D0070B
Effective Date: January 1, 2022

Instructions for Use

Table of Contents Page

Related Commercial Policies

- Provider Administered Drugs – Site of Care

Coverage Rationale

See Benefit Considerations

Ryplazim (plasminogen, human-tvmh) is proven and medically necessary for the treatment of plasminogen deficiency type 1 (hypoplasminogenemia) when the following criteria are met:[1,2]

- For initial therapy, all of the following:
  - Diagnosis of hypoplasminogenemia as measured by plasminogen activity level ≤ 50% of laboratory standard; and
  - Abnormal plasminogen antigen plasma level < 9 mg/dL as confirmed by an enzyme-linked immunosorbent assay; and
  - Presence of clinical signs and symptoms of the disease (e.g., ligneous conjunctivitis, gingivitis, tonsillitis, abnormal wound healing, etc.); and
  - Prescribed by or in consultation with a hematologist; and
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling; and
  - Initial authorization will be for no more than 6 months.
- For continuation of therapy, all of the following:
  - Patient has previously received treatment with Ryplazim therapy; and
  - Patient has experienced a positive clinical response to Ryplazim therapy (e.g., improved (reduction) in lesion number/size, improvement in wound-healing, plasminogen activity trough level has increased by at least 10 percentage points from baseline; etc.); and
  - Prescribed by or in consultation with a hematologist; and
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling; and
  - Reauthorization will be for no more than 12 months.

Ryplazim is unproven and not medically necessary for the treatment of idiopathic pulmonary fibrosis.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may

require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics

Diagnosis Code	Description
E88.02	Plasminogen deficiency

Background

Plasminogen is a naturally occurring protein synthesized by the liver. Plasminogen is converted to plasmin, which then leads to lysis of fibrin clots in the blood and/or on cell surfaces (wound healing, angiogenesis, tissue remodeling, etc.).

Plasminogen deficiency type 1, or hypoplasminogenemia, is a rare autosomal-recessive disorder of the fibrinolytic system. Deficiency of plasminogen levels cause abnormal extravascular accumulation or growth of fibrin-rich ligneous pseudomembranous lesions on mucous membranes throughout the body. Consequently, the most common clinical manifestation of plasminogen deficiency type 1 is ligneous conjunctivitis (LC), characterized by inflamed, woody growth on the conjunctival membranes – which, if left untreated, may result in visual impairment or blindness. Replacement therapy may increase the plasma level of plasminogen, thereby allowing a temporary correction of the deficiency and reduction of extravascular fibrinous lesions.[2-4]

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

Clinical Evidence

The efficacy of plasminogen, human-tvmh in pediatric and adult patients with plasminogen deficiency type 1 was evaluated in RYPLAZIM trial 2, a single-arm, open-label clinical trial (n = 15). Enrolled patients, aged 4 to 42 years, had a baseline plasminogen activity level between <5% and 45% of normal, and biallelic mutations in the *plasminogen (PLG)* gene. All patients received plasminogen, human-tvmh at a dose of 6.6 mg/kg administered every 2 to 4 days for 28 weeks, with a primary endpoint of achieving at least an increase of individual trough plasminogen activity by an absolute 10% above baseline. Secondary endpoint was establishment of overall rate of clinical success at 48 weeks, defined by patients with visible [sites mainly located in the eyes, nose, gums, hands and feet] or measurable non-visible lesions [cervix, bronchus, colon, vagina and uterus] achieving ≥50% improvement in lesion number/size, or functionality impact from baseline. Authors found that 78% of external lesions and 75% of internal lesions were resolved by week 48, with no recurrent or new external or internal lesions in any patient through week 48 (NCT02690714).[1-2]

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Ryplazim® (plasminogen, human-tvmh) is plasma-derived human plasminogen indicated for the treatment of patients with plasminogen deficiency type 1 (hypoplasminogenemia).[1]

References

1. Ryplazim [prescribing information]. Rockville, MD: ProMetic BioTherapeutics, Inc.; June 2021.
2. Shapiro AD, Nakar C, Parker JM, et al. Plasminogen replacement therapy for the treatment of children and adults with congenital plasminogen deficiency. Blood. 2018 Jan 10.
3. Tefs K, Gueorguieva M, Klammt J, et al. Molecular and clinical spectrum of type I plasminogen deficiency: A series of 50 patients. Blood. 2006 Nov 1;108(9):3021-6.
4. Schuster V, Hügle B, Tefs K. Plasminogen deficiency. J Thromb Haemost. 2007 Dec;5(12):2315-22.

Policy History/Revision Information

Date	Summary of Changes
01/01/2022	**Coverage Rationale** • Removed reference link to the Medical Benefit Drug Policy titled *Review at Launch for New to Market Medications* • Revised coverage criteria: *Initial Therapy* ○ Added criterion to require: ▪ Abnormal plasminogen antigen plasma level < 9 mg/dL as confirmed by an enzyme-linked immunosorbent assay ▪ Ryplazim is prescribed by or in consultation with a hematologist ○ Replaced criterion requiring: ▪ "Diagnosis of hypoplasminogenemia as measured by plasminogen activity level ≤ *45*% of laboratory standard" with "diagnosis of hypoplasminogenemia as measured by plasminogen activity level ≤ *50*% of laboratory standard" ▪ "Initial authorization will be for no more than *12* months" with "initial authorization will be for no more than *6* months" *Continuation of Therapy* ○ Updated list of examples of a positive clinical response to Ryplazim therapy; added "plasminogen activity trough level has increased by at least 10 percentage points from baseline" ○ Added criterion to require Ryplazim is prescribed by or in consultation with a hematologist **Supporting Information** • Archived previous policy version 2021D0070A

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent

professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.