Ryplazim® (Plasminogen, Human-Tvmh)

Policy Number: PHARMACY 340.1 T0
Effective Date: October 1, 2021

➲ Instructions for Use

Table of Contents Page

Coverage Rationale 1
Prior Authorization Requirements 2
Applicable Codes 2
Background 2
Benefit Considerations 2
Clinical Evidence 3
U.S. Food and Drug Administration 3
References 3
Policy History/Revision Information 3
Instructions for Use 3

Related Policies

- Acquired Rare Disease Drug Therapy Exception Process
- Drug Coverage Guidelines
- Provider Administered Drugs – Site of Care
- Review at Launch for New to Market Medications

Coverage Rationale

➲ See Benefit Considerations

Ryplazim (plasminogen, human-tvmh) has been added to the Review at Launch program. Some members may not be eligible for coverage of this medication at this time. Refer to the Clinical policy titled Review at Launch for New to Market Medications for additional details.

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 ≤ 45% of laboratory standard; and
  - Presence of clinical signs and symptoms of the disease (e.g., ligneous conjunctivitis, gingivitis, tonsillitis, abnormal wound healing, etc.); and
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling; and
  - Initial authorization will be for no more than 12 months.
- For continuation 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, etc.); 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.

Prior Authorization Requirements

- Prior to Jan. 1, 2022: Prior authorization is not required, however it is strongly recommended for Ryplazim. While no penalty will be imposed for failure to request a pre-service review, if one is not requested, a medical necessity review will be conducted post-service to determine coverage. It is the referring physician's responsibility to provide medical documentation to demonstrate clinical necessity for the medication. Refer to the Clinical Policy titled Review at Launch for New to Market Medications.
- On or after Jan. 1, 2022: Prior authorization is required in all sites of service.

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 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 hypolasminogenemia, 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 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; refer to the Administrative Policy titled Acquired Rare Disease Drug Therapy Exception Process.

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

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealth Group National Pharmacy & Therapeutics Committee. [*2021D0070A*]

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
10/01/2021	• New Clinical Policy

Instructions for Use

This Clinical Policy provides assistance in interpreting UnitedHealthcare Oxford 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 Oxford reserves the right to modify its Policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice.

The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Oxford Clinical 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.