BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

RHAPSIDO® (remibrutinib) oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Rhapsido (remibrutinib) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Allergist or Immunologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **chronic spontaneous urticaria (CSU)** that is symptomatic despite second generation H1 antihistamine treatment

4. Individual has itch and hives on most days of the week for at least 6 consecutive weeks over the last 6 months

5. Individual does not have other forms of urticaria or other skin diseases with chronic itching other than those associated with CSU (see Definitions section)

6. Rhapsido (remibrutinib) is not indicated for the treatment of other forms of urticaria (see Definitions section)

7. Individual has completed **ALL** the following **baseline tests** before initiation of treatment and will have continued monitoring as clinically appropriate:
    a. Weekly urticaria activity score (UAS7) score of 16 or more
    b. Weekly itch severity score (ISS7) score of 6 or more
    c. Weekly hive count score (HSS7) score of 6 or more

8. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

9. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **TWO** the following:
    a. At least a 2 week trial of non-sedating H1 antihistamine at four times the FDA-approved dose
    b. At least a 2 week trial of non-sedating H1 antihistamine in combination with a H2 antihistamine
    c. At least a 4 week trial to a leukotriene modifiers (e.g., montelukast, zafirlukast) in combination with an H1 antihistamine

10. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **BOTH** of the following:
    a. Xolair (omalizumab)
    b. Dupixent (dupilumab)

11. Individual does not have any hepatic impairment (Child-Pugh Class A-C)

12. There will not be concurrent use of **ANY** of the following:
    a. Live or live-attenuated vaccines
    b. Strong or moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole, diltiazem, verapamil, amiodarone, Itraconazole, Ketoconazole, others)
    c. Strong or moderate CYP3A4 inducers (e.g., dabrfenib, dexamethasone, nafcillin, rifampin, rifabutin, phenobarbital, carbamazepine, others)
    d. Anticoagulants

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Rhapsido (remibrutinib) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

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1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Allergist or Immunologist

2. Individual has documentation of positive clinical response to therapy defined as achieved and maintains **TWO** of the following:
    a. Decrease in severity of itching
    b. Decrease in number of hives
    c. Decrease in size of hives
    d. Decrease in frequency urticaria episodes

3. Individual has been adherent with the medication

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual does not have other forms of urticaria or other skin diseases with chronic itching other than those associated with CSU

6. Individual has not developed any significant adverse drug effects that may exclude continued use such as significant mucocutaneous-related bleeding

7. Individual does not have any hepatic impairment (Child-Pugh Class A-C)

8. There will not be concurrent use of **ANY** of the following:
    a. Live or live-attenuated vaccines
    b. Strong or moderate CYP3A4 inhibitors
    c. Strong or moderate CYP3A4 inducers
    d. Anticoagulants

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

    1. **Off-Label Use of Non-Cancer Medications**

    2. **Off-Label Use of Cancer Medications**

Description:

Rhapsido (remibrutinib) is indicated for the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment. Rhapsido (remibrutinib) is not indicated for other forms of urticaria.

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Remibrutinib is an oral, small molecule kinase inhibitor that inhibits Bruton's tyrosine kinase (BTK). BTK is an intracellular protein expressed in mast cells, basophils, B cells, macrophages, and thrombocytes. BTK is involved in intracellular signaling via Fc epsilon receptor-1 (FcεR1), Fc gamma receptors (FcγR), and the B cell antigen receptor (BCR). Remibrutinib also inhibits the BTK-related kinases tec protein tyrosine kinase (TEC) and BMX non-receptor tyrosine kinase (BMX). Remibrutinib inhibits mast cell and basophil degranulation, including release of histamine and other proinflammatory mediators, mediated by pathogenic IgE or IgG directed against the FcεR1 or IgE.

Chronic spontaneous urticaria (CSU) is defined by the presence of recurrent urticaria, angioedema, or both for a period of six weeks or longer. CSU is self-limited, with an average duration of two to five years, but symptoms can significantly impact the quality of life. The urticarial lesions (also called hives or wheals) can vary in size and are usually surrounded by erythema. They are associated with an itching sensation that is usually limited to 30 minutes to 24 hours in duration. Disease severity is measured by a weekly urticaria activity score (UAS7, range 0–42), which is a composite of a weekly itch severity score (ISS7, range 0–21) and a weekly hive count score (HSS7, (range 0–21). The ISS7 score is the sum of the daily itch severity scores (ISS), scored from 0 to 3, recorded at the same time of the day for a 7-day period. Standard treatments include a second-generation H1 antihistamine which can be increased in dose or combined with other antihistamines or a leukotriene modifier. Short courses of steroids may be warranted but are usually avoided long-term. Individuals' refractory to H1 antihistamine regimens, may benefit from Dupixent (dupilumab) or Xolair (omalizumab).

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Chronic Spontaneous Urticaria (CSU)
Weekly Itch Severity Score (ISS7)

- The ISS7 is the sum of the daily itch severity scores (daily ISS) over 7 days and ranges from 0-21
- The daily ISS is the average of the AM & PM scores on a scale of 0 (none) to 3 (severe) [0 = none; 1 = mild; 2 = moderate; 3 = severe]
- A higher itch severity score indicates more severe itching
- A negative change score indicates improvement
- Minimally important difference (MID) response in the ISS7
    - MID response is defined as a reduction ≥ 5 points in ISS7

Urticaria activity score over 7 days (UAS7) – a composite scoring

- The UAS7 is the sum of the daily urticarial activity scores (daily UAS) over 7 days and ranges from 0-42
- The daily UAS is the average of the AM & PM urticarial activity scores and ranges from 0 to 6
- The urticarial activity score is the sum of ratings on a scale of 0 to 3 (0 = none; 1 = mild; 2 = moderate; 3 = intense/severe) for:
    - (1) HSS7 is the number of wheals (hives)
        - 0 = none
        - 1 = mild (1-6 hives)
        - 2 = moderate (7-12 hives)
        - 3 = severe (more than 12 hives)

  - (2) itch intensity (ISS) over the previous 12 hours, ranges from 0 to 6, and is measured twice daily (morning & evening)
    - 0 = none
    - 1 = mild (present but not annoying or troublesome)
    - 2 = moderate (troublesome but does not interfere with normal daily activity or sleep)
    - 3 = intense (severe, sufficiently troublesome to interfere with normal daily activity or sleep)
- A higher urticarial activity score indicates more urticaria activity
- A negative change score indicates improvement
- Goal is UAS7 score $\leq$ 6
- Complete responder is UAS7 = 0

H1 Antihistamines:
- First-generation agents (e.g., hydroxyzine, diphenhydramine, chlorpheniramine)
- Second-generation agents (e.g., cetirizine, levocetirizine, fexofenadine, loratadine, desloratadine)

H2 Antagonist:
- Cimetidine, famotidine

Leukotriene receptor antagonists:
- Montelukast, zafirlukast

Other forms of urticaria or other skin diseases with chronic itching other than those associated with CSU:
- Sole trigger of chronic urticaria (chronic inducible urticaria) including urticaria factitial (symptomatic dermographism), cold-, heat-, solar-, pressure-, delayed pressure-, aquagenic-, cholinergic-, or contact-urticaria
- Other diseases with symptoms of urticaria or angioedema, including but not limited to urticaria vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary urticaria, or drug-induced urticaria
- Skin disease associated with chronic itching e.g. atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus or psoriasis

Resources:

Rhapsido (remibrutinib) product information, revised by Novartis Pharmaceuticals Corporation 09-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed October 19, 2025.

Saini S. Chronic spontaneous urticaria: Clinical manifestations, diagnosis, pathogenesis, and natural history. In: UpToDate, Callen JP, Hussain Z, Feldweg A (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through September 2025. Topic last updated May 30, 2025. Accessed October 19, 2025.

Khan DA. Chronic spontaneous urticaria: Standard management and patient education. In: UpToDate, Saini S, Callen JP, Hussain Z, Feldwg AM (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through September 2025. Topic last updated June 05, 2025. Accessed October 19, 2025.

Khan DA. Chronic spontaneous urticaria: Treatment of refractory symptoms. In: UpToDate, Saini S, Callen JP, Feldwg AM (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through September 2025. Topic last updated May 07, 2025. Accessed October 19, 2025.

Metz M, Gimenez-Arnau A, Hide M, et al.: Remibrutinib in Chronic Spontaneous Urticaria. N Engl J Med 2025 March 06;392 (10):984-994.DOI: 10.1056/NEJMoa2408792. Accessed October 19, 2025.

Jain V, Gimenez-Arnau A, Hayama K, et al.: Remibrutinib demonstrates favorable safety profile and sustained efficacy in chronic spontaneous urticaria over 52 weeks. J Allergy Clin Immunol 2024 Feb;153 (2):479-486

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT05030311: A Multicenter, Randomized, Double-blind, Placebo-controlled Phase 3 Study of Remibrutinib (LOU064) to Investigate the Efficacy, Safety and Tolerability for 52 Weeks in Adult Chronic Spontaneous Urticaria (CSU) Patients Inadequately Controlled by H1-antihistamines. Available from: http://clinicaltrials.gov. Last update posted April 08, 2025. Last verified April 2025. Accessed October 19, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT05032157: A Multicenter, Randomized, Double-blind, Placebo-controlled Phase 3 Study of Remibrutinib (LOU064) to Investigate the Efficacy, Safety and Tolerability for 52 Weeks in Adult Chronic Spontaneous Urticaria (CSU) Patients Inadequately Controlled by H1-antihistamines. Available from: http://clinicaltrials.gov. Last update posted April 08, 2025. Last verified April 2025. Accessed October 19, 2025.