09-J5000-36

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Revised: 00/00/00

Subject: Remibrutinib (Rhapsido) Tablet

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DESCRIPTION:

Remibrutinib (Rhapsido) is a Bruton tyrosine kinase (BTK) inhibitor approved by the U.S Food and Drug Administration (FDA) in September 2025 for “the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment”. Other treatments FDA-approved for CSU include second-generation H1 antihistamines, and the injectable biologics of omalizumab (Xolair) (approved for CSU in March 2014) and dupilumab (Dupixent) (approved for CSU in April 2025). Remibrutinib is the first oral non-antihistamine, and first BTK inhibitor, to be FDA-approved for the treatment of CSU.

Chronic Spontaneous Urticaria (CSU)

Chronic spontaneous urticaria (CSU), also referred to as chronic urticaria (CU) or chronic idiopathic urticaria (CIU), is a mast cell-mediated condition that involves the recurrent spontaneous occurrence of urticaria and/or angioedema. Urticaria is characterized by the development of wheals (hives), angioedema, or both. CSU is defined by the presence of urticaria for more than 6 weeks with no definite eliciting factor involved. Signs and symptoms may occur daily or follow an intermittent/recurrent course. Routine diagnostic tests (e.g., blood tests for complete blood count and inflammatory markers, skin prick test) are mainly used to rule out other potential diseases and not to confirm the diagnosis. Medication that is suspected to worsen the disease (e.g., NSAIDs) should be discontinued or substituted by another class of agents to reduce disease exacerbations. CSU can be a debilitating condition that significantly impairs a patient's quality of life, and treatment goals include symptom control and normalization of quality of life for the patient.

The international European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA2LEN)/European Dermatology Forum (EDF)/Asia Pacific Association of

Allergy, Asthma and Clinical Immunology (APAAACI) guideline recommends the following algorithm for the treatment of CSU:

- First-line treatment: Second-generation H1-antihistamine at standard dosing, dosed daily (e.g., cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine)
- Second-line treatment: If inadequate control at standard dosing, increase the daily dose of the second-generation H1-antihistamine to up to 4 times the standard dosing before other treatments are considered
- Third-line treatment: If inadequate control after 2 to 4 weeks of therapy with a high dose second-generation H1-antihistamine, add on omalizumab

High dose second-generation H1-antihistamine therapy has been suggested in guidelines since the year 2000, and no serious adverse events or side effects from long-term use or potential accumulation have been reported. Treatment for CSU should be evaluated every 3 to 6 months to assess disease activity, impact, and control. The severity of urticaria can fluctuate, including the possibility of spontaneous remission. In addition, patients should be assessed for any side effects of treatment. If an adjustment to treatment is warranted, it may include stepping up therapy, changing medication due to side effects, or stepping down treatment if the patient has been symptom free for 3 to 6 months.

Omalizumab was approved for the treatment of CSU in 2014 and has since received placement in treatment guidelines. However, for some patients omalizumab provides partial or no improvement in their signs and symptoms. Current guidelines support using cyclosporine as add-on therapy for patients with severe disease and an incomplete response to omalizumab and an antihistamine used in combination, but it is not recommended as standard treatment due to the risk and incidence of adverse effects. Dupilumab has been shown to be an effective treatment for CSU per the LIBERTY CUPID CSU studies, but its place in treatment guidelines has yet to be established. The LIBERTY CSU CUPID-B trial was designed to determine if dupilumab is an effective alternative in patients with a lack of response to omalizumab, incomplete control of their CSU while taking omalizumab, or an inability to tolerate the use of omalizumab. The dupilumab group in this study did not meet statistical significance for reduction in the primary endpoint of change from baseline in itch severity score over 7 days (ISS7) at Week 24

Efficacy

The efficacy of Rhapsido for chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment was evaluated in two identical, 52-week, multi-center, randomized, double-blind, placebo-controlled clinical trials (REMIX-1 [NCT05030311] and REMIX-2 [NCT05032157]). REMIX-1 and REMIX-2 enrolled a total of 925 adult patients, diagnosed with CSU inadequately controlled despite treatment with H1 antihistamines, as defined by the presence of itch and hives for at least 6 consecutive weeks. All patients were required to have a weekly urticaria activity score (UAS7) of greater than or equal to 16 (range 0-42), a weekly itch severity score (ISS7) of greater than or equal to 6 (range 0-21) and a weekly hives severity score (HSS7) of greater than or equal to 6 (range 0-21) for 7 days prior to randomization. In REMIX-1 and REMIX-2, 32% and 31% of patients had previous exposure to an anti-IgE biologic (e.g., omalizumab), respectively. Patients were randomized in a 2:1 ratio to receive either Rhapsido 25 mg or placebo, in addition to background therapy with an H1 antihistamine, orally twice daily for 24 weeks during the double-blind treatment period and subsequently continued in a 28-week open-label treatment period, during which all patients received

Rhapsido 25 mg twice daily. While REMIX-1 and REMIX-2 clinical trials included an open-label period, efficacy is based on results from 912 patients treated during the controlled period of 24 weeks.

The co-primary endpoints were absolute change from baseline in ISS7 and HSS7 at Week 12. The ISS7 (range 0 to 21) was defined as the sum of the daily itch severity scores (range 0 to 3) recorded over a 7-day period. The HSS7 (range 0 to 21) was defined as the sum of the daily hive severity scores (range 0 to 3) recorded over a 7-day period. In both REMIX-1 and REMIX-2 studies, the co-primary endpoints showed statistically significant improvement in itch and hives symptoms in patients treated with Rhapsido compared to patients treated with placebo. Improvements in ISS7 and HSS7 at Week 12 were consistent regardless of patients' baseline total IgE level.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of remibrutinib (Rhapsido) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "6"):

1. **BOTH** of the following ("a", "b", or "c"):
    a. Remibrutinib will be used for the treatment of an indication listed in the Table, and **ALL** of the indication-specific criteria are met
    b. **EITHER** of the following if the member has an FDA-approved indication ("i" or "ii"):
        i. The member's age is within FDA labeling for the requested indication for remibrutinib
        ii. The prescriber has provided information in support of using remibrutinib for the member's age for the requested indication
2. If the member has a diagnosis of chronic spontaneous urticaria (CSU) [otherwise known as chronic idiopathic urticaria [CIU]], then **ONE** of the following ("a" or "b"):
    a. **BOTH** of the following ("i' and "ii"):
        i. The member is currently treated with second-generation H1-antihistamine therapy (e.g., cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine)
        ii. The member will continue second-generation H1-antihistamine therapy in combination with remibrutinib
    b. The member has an intolerance, hypersensitivity, or FDA labeled contraindication to **ALL** second-generation H1-antihistamines
3. The prescriber is a specialist in the area of the member's diagnosis (e.g., dermatologist, allergist, immunologist), **OR** the prescriber has consulted with a specialist in the area of the member's diagnosis
4. The member does **NOT** have any FDA-labeled contraindications to Rhapsido

5. The member will **NOT** be using remibrutinib in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Anzupgo (delgocitinib), Cibinqo (abrocitinib), Leqselvi (deuruxolitinib), Litfulo (ritlecitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Olumiant (baricitinib), Rinvoq/Rinvoq LQ (upadacitinib), and Xeljanz/Xeljanz XR (tofacitinib)]; Otezla/Otezla XR (apremilast); Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]
6. **ONE** of the following ("a", "b", or "c"):
    a. The requested quantity (dose) does **NOT** exceed 25 mg twice daily
        - QL: 25 mg tablets – 60 tablets/30 days (2 tablets/day)
    b. The requested quantity (dose) exceeds the program quantity limit but does **NOT** exceed the maximum FDA labeled dose for the requested indication, **AND** there is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does **NOT** exceed the program quantity limit
    c. The requested indication does **NOT** have a maximum FDA labeled dose, **AND** there is support for therapy with a higher dose for the requested indication

Approval duration: 12 months

Table 1

Indications and Specific Criteria	
Indication	**Specific Criteria**
Chronic spontaneous urticaria (CSU) [otherwise known as chronic idiopathic urticaria (CIU)]	When **ALL** of the following are met ("1" to "4"): 1. The member has had hives and itching for more than 6 weeks **AND** 2. The prescriber has evaluated the member to determine if the member is currently treated with medications known to cause or worsen urticaria (e.g., NSAIDs) in order to reduce urticaria risk **AND** 3. The member has **ONE** of the following ("a", "b", or "c"): a. Has tried and had an inadequate response to the FDA-labeled maximum dose of **ONE** second-generation H-1 antihistamine (e.g., cetirizine, levocetirizine, fexofenadine, loratadine, desloratadine) after at least a 2-week duration of therapy, **AND ONE** of the following: i. The member has tried and had an inadequate response to a maximally tolerated dose of **ONE** second-generation H1-antihistamine titrated up to 4 times above the FDA labeled maximum dose after at least a 2-week duration of therapy **OR**

	ii. There is support that the member cannot be treated with a second-generation H-1 antihistamine at a dose above the FDA labeled maximum dose **OR** b. An intolerance or hypersensitivity to therapy with **ONE** second-generation H-1 antihistamine **OR** c. An FDA labeled contraindication to **ALL** second-generation H-1 antihistamines **AND** 4. **ANY** of the following (submitted medical records/chart notes are required for confirmation): a. The member has tried and had an inadequate response to **BOTH** dupilumab (Dupixent) **AND** omalizumab (Xolair) after at least a 3-month trial per product **OR** b. The member has tried and had an inadequate response to **EITHER** dupilumab (Dupixent) **OR** omalizumab (Xolair) after at least a 3-month trial, **AND** an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration), hypersensitivity, or FDA-labeled contraindication to **EITHER** dupilumab (Dupixent) **OR** omalizumab (Xolair) **OR** c. The member has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration), hypersensitivity, or FDA-labeled contraindication to **BOTH** dupilumab (Dupixent) **AND** omalizumab (Xolair)

Continuation of remibrutinib (Rhapsido) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "7"):

1. An authorization or reauthorization for remibrutinib has been previously approved by Florida Blue [Note: members not previously approved for the requested agent will require initial evaluation review]
2. The member has had clinical benefit with remibrutinib
3. If the member has a diagnosis of chronic spontaneous urticaria (CSU) [otherwise known as chronic idiopathic urticaria [CIU]], then **ONE** of the following ("a" or "b"):
    a. The member will continue second-generation H1-antihistamine therapy (e.g., cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine) in combination with remibrutinib

b. The member has an intolerance, hypersensitivity, or FDA labeled contraindication to **ALL** second-generation H1-antihistamines

4. The prescriber is a specialist in the area of the member's diagnosis (e.g., dermatologist, allergist, immunologist), **OR** the prescriber has consulted with a specialist in the area of the member's diagnosis
5. The member does **NOT** have any FDA-labeled contraindications to Rhapsido
6. The member will **NOT** be using remibrutinib in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Anzupgo (delgocitinib), Cibinqo (abrocitinib), Leqselvi (deuruxolitinib), Litfulo (ritlecitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Olumiant (baricitinib), Rinvoq/Rinvoq LQ (upadacitinib), and Xeljanz/Xeljanz XR (tofacitinib)]; Otezla/Otezla XR (apremilast); Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]
7. **ONE** of the following ("a", "b", or "c"):
   a. The requested quantity (dose) does **NOT** exceed 25 mg twice daily
      - QL: 25 mg tablets – 60 tablets/30 days (2 tablets/day)

      OR

   b. The requested quantity (dose) exceeds the program quantity limit but does **NOT** exceed the maximum FDA labeled dose for the requested indication, **AND** there is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does **NOT** exceed the program quantity limit

      OR

   c. The requested indication does **NOT** have a maximum FDA labeled dose, **AND** there is support for therapy with a higher dose for the requested indication

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Indicated for the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment. Limitations of Use (per package insert): Not indicated for other forms of urticaria.
- Recommended dosage is 25 mg orally twice daily with or without food. Swallow tablets whole. Do not split, crush, or chew. Interrupt remibrutinib for 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Dose Adjustments

- Renal Impairment - Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.
- Hepatic Impairment - Avoid remibrutinib use in individuals with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment.

Drug Availability

- 25 mg film-coated tablets in a 60-count bottle
- Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Dispense and store in the original container in order to protect from moisture.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- **Risk of Bleeding**: Monitor for signs and symptoms of bleeding. Interrupt treatment with remibrutinib if bleeding is observed or pre- and post-surgery. Concomitant use of antithrombotic agents with remibrutinib may further increase risk of bleeding.
- **Live Attenuated Vaccines**: Avoid live or live-attenuated vaccines in patients receiving remibrutinib.

BILLING/CODING INFORMATION:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, NOS

ICD-10 Diagnosis Codes That Support Medical Necessity

L50.8	Other urticaria

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

None

RELATED GUIDELINES:

Dupilumab (Dupixent), 09-J2000-80

Omalizumab (Xolair), 09-J0000-44

OTHER:

NOTE: The list of biologic immunomodulator agents not permitted as concomitant therapy can be found at Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy.

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6. Rhapsido (remibrutinib tablet) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; September 2025.
7. Zuberbier, T, Abdul Latiff, AH, Abuzakouk, M, et al. The international EAACI/GA^2LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022;77(3):734–766.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 02/11/26.

GUIDELINE UPDATE INFORMATION:

04/01/26	New Medical Coverage Guideline.