New Drug Overview

Rhapsido (remibrutinib)

PDL Category: Immunological Agents

Introduction

Disease Background:

- Chronic urticaria is described as temporary wheals of less than 24 hours in duration that occur with or without angioedema and recur either continuously or intermittently for greater than 6 weeks (*Cindy 2025*).
  - Chronic urticaria can be spontaneous or inducible urticarias.
    - Chronic spontaneous urticaria (CSU) is defined as urticaria, with or without angioedema, that occurs with no definite prompt and is described by a period of less than 24 hours for individual wheals but with continuous or intermittent activity for more than 6 weeks.
      - It is estimated that most with chronic urticaria have CSU (80-90%).
      - Note that international guidelines, since 2017, have supported the definition of CSU to include isolated idiopathic angioedema without urticaria, as long as other angioedema conditions have been excluded (*Saini 2025*).
    - Inducible urticaria entails requiring a specific trigger to prompt urticaria and/or angioedema. It may be physical or nonphysical (*Cindy 2025*).
      - Physical stimuli may include heat, cold, exercise, and sunlight (*Saini 2025*).
- Up to 1 percent of the United States population can be affected with CSU at any period of time (*Saini 2025*).
  - While it can occur in both adults and children, it is more common in adults and occurs twice as often in women than men.
- Urticaria encompasses the release of histamine and other agents in the dermis, while release in deeper parts of the dermis causes angioedema. Mast cells and basophils are the main inflammatory cells implicated in urticaria (*Cindy 2025*).
- While most patients have clinical symptoms that are confined to the skin, some report additional systemic symptoms (*Saini 2025*).
  - Cutaneous symptoms include
    - Urticarial lesions, which are also called hives or wheals. They may present with erythema and create an itchy sensation.
    - Angioedema, if does occur, is generally submucosal or subcutaneous swelling and affects parts of the body that may include the lips, cheeks, extremities, or genitals.
  - Some may experience systemic symptoms, which may include headache, fatigue, malaise, wheezing, flushing, palpitations, or gastrointestinal symptoms.
- Management of CSU generally starts with the use of oral second-generation H1 antihistamines (*Cindy 2025*).
- Rhapsido was FDA approved in 2025.

Pharmacology/Usage

- Rhapsido (remibrutinib) is a kinase inhibitor. It 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.

Indications

Table 1. Food and Drug Administration Approved Indications

Indication	Rhapsido (remibrutinib)
• For the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment. [a]	✔

[a] Limitation of use includes that Rhapsido is not indicated for other forms of urticaria.

(Prescribing information: Rhapsido 2025)

- Information on indications, mechanism of action, pharmacokinetics, dosing, safety, and clinical efficacy summary has been obtained from the prescribing information for the individual products, except where noted otherwise.

Dosing and administration

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Rhapsido (remibrutinib)	Film-Coated Tablets	Oral	Twice daily, with or without food.	• Swallow tablets whole with water; do not split, crush, or chew. • If a dose or doses is missed, skip the missed dose, and take the next dose at its regularly scheduled time. Do not take an extra dose(s) to make up for a missed dose(s). • Interrupt treatment for 3 to 7 days pre- and post-surgery depending on the type of surgery and the risk of bleeding. • Avoid use of Rhapsido with mild, moderate, or severe hepatic impairment.

See the current prescribing information for full details.

Clinical Efficacy Summary

- The efficacy of Rhapsido was assessed in two identical, 52-week, multicenter, randomized, double-blind, placebo-controlled studies (REMIX-1 and REMIX-2).
  - The studies enrolled adults (N=925) diagnosed with CSU inadequately controlled despite treatment with H1 antihistamines, as defined by the presence of itch and hives for ≥6 consecutive weeks.

- All patients were required to have a weekly urticaria activity score (UAS7) ≥16 (range 0-42), a weekly itch severity score (ISS7) ≥6 (range 0-21), and a weekly hives severity score (HSS7) ≥6 (range 0-21) for 7 days prior to randomization.
- Patients were randomized to receive either Rhapsido or placebo for 24 weeks during the double-blind treatment period and subsequently continued in a 28-week open-label treatment period, where all patients received Rhapsido 25mg BID.
- While both studies included an open-label period, efficacy is based on results from 912 patients treated during the controlled period of 24 weeks.

- In REMIX-1, the mean age of included patients (N=462) was 45 years, with 91% being 18 to 65 years of age and 9% being >65 years of age. In addition, 68% were female and 58% were White.
  - Regarding disease characteristics, 65% had a UAS7 ≥28, the mean HSS7 score was 16, the mean ISS7 score was 15, 52% had previous experience of angioedema, and 32% had previous exposure to anti-IgE biologics.
- In REMIX-2, the mean age of included patients (N=450) was 42 years, with 92% being 18 to 65 years of age and 8% being >65 years of age. In addition, 65% were female and 52% were White.
  - Regarding disease characteristics, 60% had a UAS7 ≥28, the mean HSS7 score was 16, the mean ISS7 score was 14, 46% had previous experience of angioedema, and 31% had previous exposure to anti-IgE biologics.
- The reported mean duration of CSU at enrollment across treatment groups was 6.6 and 5.2 years in the REMIX-1 and REMIX-2 studies, respectively, with 39% and 29% of the patients having a duration of CSU >5 years.
- 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.
- The key secondary endpoint was absolute change from baseline in UAS7 at week 12.
  - The UAS7 (range 0 to 42) was a composite of the ISS7 and HSS7.
- Secondary endpoints included the proportion of patients who achieved UAS7 ≤6 at weeks 2 and 12, and the proportion of patients who achieved complete absence of itch and hives (UAS7 = 0) at week 12.
- In both studies, the co-primary and all secondary endpoints demonstrated statistically significant improvement in itch and hives symptoms in patients treated with Rhapsido as compared to patients treated with placebo.
  - Results are presented in the table below, which was adapted from the prescribing information.

Table 3. Efficacy results

	REMIX-1		**REMIX-2**	
	Rhapsido (N=309)	**Placebo (N=153)**	**Rhapsido (N=297)**	**Placebo (N=153)**
Change from Baseline in ISS7 at week 12				
Least Squares (LS) Mean change from baseline (CFB)	-9.52	-6.89	-8.95	-5.72
Difference in LS mean vs placebo	-2.63		-3.23	
95% confidence interval (CI) for difference	-3.70, -1.56		-4.29, -2.16	

	REMIX-1		REMIX-2	
	Rhapsido (N=309)	**Placebo (N=153)**	**Rhapsido (N=297)**	**Placebo (N=153)**
Change from Baseline in HSS7 at week 12				
LS Mean CFB	-10.47	-6.86	-10.47	-6.00
Difference in LS mean vs placebo	-3.61		-4.47	
95% CI for difference	-4.85, -2.36		-5.71, -3.23	
Change from Baseline in UAS7 at week 12				
LS Mean CFB	-20.02	-13.79	-19.41	-11.73
Difference in LS mean vs placebo	-6.22		-7.68	
95% CI for difference	-8.45, -4.00		-9.91, -5.46	
Proportion of patients with UAS7 ≤6 at week 2				
n (%)	104 (33.7%)	5 (3.3%)	89 (30%)	9 (5.9%)
Treatment difference	30.20		24.55	
95% CI	24.30, 36.10		18.31, 30.80	
Proportion of patients with UAS7 ≤6 at week 12				
n (%)	154 (49.8%)	38 (24.8%)	139 (46.8%)	30 (19.6%)
Treatment difference	25.44		27.61	
95% CI	16.48, 34.39		19.14, 36.08	
Proportion of patients with UAS7 = 0 at week 12				
n (%)	96 (31.1%)	16 (10.5%)	83 (27.9%)	10 (6.5%)
Treatment difference	20.55		21.60	
95% CI	13.35, 27.75		15.10, 28.10	

Clinical guidelines

- Note that the guidelines have not been updated to include Rhapsido as they were published prior to FDA approval of Rhapsido.
- **The International European Academy of Allergology and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA^{2}LEN)/European Dermatology Forum (EDF; EuroGuiDerm)/Asia Pacific Association of Allergy, Asthma, and Clinical Immunology (APAAACI) guideline for the definition, classification, diagnosis, and management of urticaria, 2022** (*Zuberbier et al 2022*).
  - The authors recommend to aim for complete symptom control in urticaria and in patients with CSU to discontinue medications that may make the disease worse (ie NSAIDs).
  - A second generation H1-antihistamine is recommended as first-line treatment for all types of urticaria.
  - For second-line treatment, it is recommended to increase the second generation antihistamine dose up to 4-fold if the chronic urticaria is not responsive to standard doses instead of considering other agents.
  - It is suggested to use the antihistamines regularly for chronic urticaria and it is suggested to not use various antihistamines at the same time.
  - It is recommended to add omalizumab (currently licensed for CSU) if patients with chronic urticaria are not responding to high-dose second generation antihistamines.
  - It is suggested to use ciclosporin (as add-on treatment) if patients with chronic urticaria are not responding to high-dose second generation antihistamines and omalizumab.
- **The European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA^{2}LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO) guideline for the definition, classification, diagnosis, and management of urticaria** (*Zuberbier et al 2018*).
  - This guideline recommends aiming at complete symptom control in urticaria and for patients with CSU to discontinue medication that is thought to worsen the disease (ie NSAIDs).
  - It is suggested to use second generation H1-antihistamines rather than first generation for chronic urticaria and second generation H1-antihistamines are recommended as first-line treatment of chronic urticaria, which should be taken continuously rather than as needed.
  - It is recommended to not use various H1-antihistamines at the same time.
  - It is suggested to increase the dose up to fourfold if not responsive to lower doses of the second generation H1-antihistamine with chronic urticaria.
  - It is recommended to add omalizumab if patients are not response to second generation H1-antihistamines for chronic urticaria.
  - It is suggested to add ciclosporin A if patients are not responsive to second generation H1-antihistamines for chronic urticaria.
  - Recommendations cannot be made regarding montelukast as add-on treatment in patients not responsive to H1-antihistamines with chronic urticaria.
- **The European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA^{2}LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO) guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update** (*Zuberbier et al 2014*).
  - This guideline recommends aiming for complete symptom control in urticaria.
  - Second generation H1-antihistamines are recommended as first-line treatment of urticaria (and recommended to be preferred over first generation H1-antihistamines).
  - A trial of up to 4-fold in the dose of the second generation H1 antihistamine is recommended as second-line treatment.
  - It is recommended these be taken continuously in the lowest dose needed instead of on demand.

- It is recommended to increase the dose of a second generation antihistamine that does not cause sedation (up to fourfold) rather than combining various antihistamines.
- Recommended third line treatments as add-on therapy to second generation H1-antihistamines include a trial of omalizumab or ciclosporin A, while montelukast is suggested as third line treatment.

- **The diagnosis and management of acute and chronic urticaria: 2014 update by the Joint Task Force on Practice Parameters (JTFPP), representing the American Academy of Allergy, Asthma, & Immunology (AAAAI); the American College of Allergy, Asthma, & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology (JCAAI)** (*Bernstein et al 2014*).
  - There is a step-wise approach to management of chronic urticaria.
    - Start with monotherapy with a second generation antihistamine and avoid triggers.
    - The second step includes one or more of the following:
      - Increasing the dose of the second generation antihistamine used in Step 1,
      - Adding another second generation antihistamine,
      - Adding an H2 antagonist,
      - Add a leukotriene receptor antagonist
      - Add a first generation antihistamine at bedtime.
    - Step 3 includes dose advancement of potent antihistamine (e.g. hydroxyzine or doxepin) as tolerated.
    - Step 4 includes adding an alternative agent, such as omalizumab, cyclosporine, or other anti-inflammatory agents, immunosuppressants, or biologics.

Safety summary

- **Contraindications:** None.

- **Box Warning:** None.

- **Warnings and precautions:**
  - In placebo-controlled studies in patients with CSU, mucocutaneous-related bleeding occurred in 9% of patients who received Rhapsido. Interrupt Rhapsido treatment if bleeding is observed and resume if the benefit is expected to outweigh the risk.
    - Use of antithrombotic agents concomitantly with Rhapsido may further increase the risk of bleeding. Consider the benefits and risks of antithrombotic agents when used concomitantly with Rhapsido. Monitor for signs and symptoms of bleeding.
  - No data are available on the effects of live or live-attenuated vaccines in patients receiving Rhapsido. The use of live and live-attenuated vaccines should be avoided in patients receiving Rhapsido.

- **Common adverse drug reactions:** Listed % incidence for adverse drug reactions= reported % incidence for drug (Rhapsido) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.
  - The most frequently reported adverse events included nasopharyngitis (2%), bleeding (7%), headache (1%), nausea (1%), and abdominal pain (1%).

- **Drug interactions:**
  - Remibrutinib is a CYP3A4 substrate.
    - Avoid use of Rhapsido with strong or moderate CYP3A4 inhibitors.

    - Avoid use of Rhapsido with strong or moderate CYP3A4 inducers.
  - Remibrutinib is a P-gp inhibitor.
    - Monitor more frequently for adverse reactions when using Rhapsido with P-gp substrates where minimal concentration changes may lead to serious adverse reactions (eg, digoxin).
  - No data are available on concomitant use of Rhapsido with anticoagulants. The concomitant use of Rhapsido and anticoagulants was not allowed in clinical studies. The use of antiplatelet agents, acetyl salicylic acid at doses up to 100mg daily or clopidogrel up to 75mg daily was allowed in the Rhapsido clinical studies.
    - Consider the risks and benefits of concomitant administration of antithrombotic agents with Rhapsido.

- **Special populations:**
  - There is no pregnancy category for this medication; however, the risk summary indicates that available data on use during pregnancy are not sufficient to assess for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.
    - There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Rhapsido during pregnancy. Pregnant women exposed to Rhapsido and healthcare providers are encouraged to contact Novartis Pharmaceuticals Corporation at 1-888-669-6682.
  - The safety and efficacy of use in the pediatric population have not been established.

Conclusion

- Chronic spontaneous urticaria (CSU) is defined as urticaria, with or without angioedema, that occurs with no definite prompt and is described by a period of less than 24 hours for individual wheals but with continuous or intermittent activity for more than 6 weeks (*Cindy 2025*).
- Rhapsido is a kinase inhibitor indicated for the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment. A limitation of use includes that Rhapsido is not indicated for other forms of urticaria.
- Interrupt Rhapsido treatment if bleeding is observed and for 3 to 7 days pre- and post-surgery or invasive procedures.
- The use of live and live-attenuated vaccines should be avoided when receiving Rhapsido treatment.
- The efficacy of Rhapsido was assessed in two identical, 52-week, multicenter, randomized, double-blind, placebo-controlled trials.
  - The co-primary efficacy endpoints were absolute change from baseline in ISS7 and HSS7 at week 12.
  - In both studies, the co-primary endpoints and all secondary endpoints demonstrated statistically significant improvement in itch and hives symptoms in patients treated with Rhapsido as compared to patients treated with placebo.
- Guidelines do not currently include Rhapsido as they were published prior to Rhapsido being FDA approved. However, first-line treatment for urticaria includes use of oral second-generation H1 antihistamines (*Zuberbier et al 2022, Zuberbier et al 2018, Zuberbier et al 2014, Bernstein et al 2014)*.

- Rhapsido is a safe and effective treatment. It is therefore recommended that Rhapsido become preferred with prior authorization to determine clinical diagnosis and parameters of use.
- **PDL Placement:**
  - ☒ Preferred with Conditions
  - ☐ Non-Preferred

References

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