Int. J. Sci. R. Tech., 2026 3(5)
A Multidisciplinary peer-reviewed Journal
www.ijsrtjournal.com [ISSN: 2394-7063]

Original Article

Clinical Review Of RHAPSIDO (Remibrutinib) In Chronic Spontaneous Urticaria

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ABSTRACT

RHAPSIDO (remibrutinib) is a selective oral Bruton's tyrosine kinase (BTK) inhibitor indicated for the treatment of chronic spontaneous urticaria (CSU) in adults who remain symptomatic despite H1-antihistamine therapy. CSU is a chronic inflammatory skin disorder characterized by recurrent wheals, intense itching, erythema, and angioedema, significantly impairing quality of life and daily functioning. Remibrutinib selectively inhibits BTK, a key intracellular enzyme involved in mast cell and basophil activation. By blocking BTK-mediated signaling, the drug suppresses histamine release and other inflammatory mediators responsible for urticaria symptoms, resulting in rapid and sustained symptom control.[1] RHAPSIDO is administered orally at a recommended dose of 25 mg twice daily with or without food. Clinical efficacy was evaluated in two identical Phase 3 randomized, double-blind, placebo-controlled trials, REMIX-1 and REMIX-2, involving 925 adult patients with CSU inadequately controlled by antihistamines. Patients receiving RHAPSIDO demonstrated significant improvements in Weekly Itch Severity Score (ISS7), Weekly Hive Severity Score (HSS7), and Weekly Urticaria Activity Score (UAS7) compared with placebo. Clinical benefits were observed as early as Week 2 and maintained through Week 24. Nearly half of the treated patients achieved well-controlled disease, while approximately one-third achieved complete symptom resolution at Week 12. The most commonly reported adverse reactions included nasopharyngitis, headache, nausea, abdominal pain, and bleeding-related events. Due to the potential risk of bleeding, caution is advised in patients receiving antithrombotic therapy or undergoing surgical procedures. Live attenuated vaccines should be avoided during treatment. Overall, RHAPSIDO represents an important advancement in targeted therapy for chronic spontaneous urticaria because of its oral administration, selective mechanism of action, rapid onset of efficacy, and sustained clinical improvement in patients inadequately controlled with conventional antihistamine therapy.[2]

Keywords: Remibrutinib, antithrombotic therapy, clinical improvement, antihistamine therapy.

INTRODUCTION

Rhapsido (remibrutinib) is a selective, oral Bruton's tyrosine kinase (BTK) inhibitor indicated for the treatment of chronic spontaneous urticaria (CSU) in adults whose symptoms remain uncontrolled despite treatment with H1-antihistamines. Chronic spontaneous urticaria is a long-lasting inflammatory skin disorder characterized by recurrent wheals (hives), intense itching, redness, and sometimes angioedema without an identifiable external trigger. The condition can significantly affect quality of life by disturbing sleep, daily activities, emotional well-being, and social functioning.

Remibrutinib acts by selectively inhibiting Bruton's tyrosine kinase, an important intracellular enzyme involved in the activation of mast cells and basophils. These immune cells release histamine and other inflammatory mediators responsible for the development of urticaria symptoms. By blocking BTK signaling, Rhapsido reduces mast cell activation and histamine release, thereby decreasing itching, swelling, and wheal formation. Its highly selective mechanism allows targeted suppression of inflammatory pathways with rapid onset of action.

Rhapsido is administered orally, usually as 25 mg tablets taken twice daily, with or without food. The drug demonstrates rapid absorption and provides sustained inhibition of BTK activity, contributing to effective symptom control in patients with chronic spontaneous urticaria. Clinical studies have shown significant improvement in urticaria activity scores, reduction in itch severity, and better overall disease

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

control in patients receiving remibrutinib therapy compared with placebo.

Common adverse effects associated with Rhapsido include headache, nausea, abdominal discomfort, dizziness, and upper respiratory tract infections. Because BTK inhibitors may influence platelet function, there is also a potential risk of bleeding. Patients receiving the medication should be monitored for signs of infection, liver function abnormalities, and hypersensitivity reactions. Careful evaluation is recommended in patients with hepatic impairment or those receiving anticoagulant therapy.

The development of remibrutinib represents an important advancement in targeted therapy for chronic inflammatory and allergic disorders. Its oral administration, selective mechanism of action, and rapid symptom relief make it a promising treatment option for patients with difficult-to-control chronic spontaneous urticaria who do not adequately respond to standard antihistamine treatment.

1. **Indications and Usage:**

RHAPSIDO is indicated for the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1-antihistamine treatment.[3]

Limitation of use:

RHAPSIDO is not indicated for other forms of urticaria.

2. **Dosage and Administration:**

a. **Recommended Dose:**

RHAPSIDO is recommended at a dose of 25 mg taken orally twice daily, with or without food. Tablets should be swallowed whole with water and should not be split, crushed, or chewed.

b. **Missed dose:**

If a dose is missed, skip the missed dose and take the next dose at the regularly scheduled time. Do not take extra doses to make up for a missed dose.

c. **Surgery:**

Temporarily interrupt RHAPSIDO treatment for 3 to 7 days before and after surgery depending on the type of surgery and bleeding risk.

3. **Dosage Forms and Strengths:**

RHAPSIDO is available as 25 mg tablets. The tablets are light yellow, round, curved, unscored, and film-coated, debossed with “LV” on one side and the Novartis logo on the other side. The tablet diameter is 7 mm.

4. **Contraindications:**

None.

5. **Warning and Precautions:**

Risk of Bleeding:

RHAPSIDO may increase the risk of bleeding. In clinical studies, mucocutaneous-related bleeding was reported in some patients receiving RHAPSIDO. Treatment should be interrupted if bleeding occurs and resumed only if the benefits outweigh the risks. RHAPSIDO should also be temporarily discontinued 3 to 7 days before and after surgery or invasive procedures. Concomitant use with antithrombotic agents may further increase bleeding risk; therefore, patients should be monitored for signs and symptoms of bleeding.[5-8]

Live Attenuated Vaccines:

The use of live or live-attenuated vaccines should be avoided in patients receiving RHAPSIDO, as no data are available regarding their safety or effectiveness during treatment.

6. **Adverse Reactions:**

Clinical Trials Experience:

The safety of RHAPSIDO was evaluated in pooled data from two identical Phase 3 clinical trials, REMIX-1 and REMIX-2, conducted in adult patients with chronic spontaneous urticaria (CSU) who remained symptomatic despite H1-antihistamine therapy. A total of 912 patients were included in the pooled safety population, with 606 patients receiving RHAPSIDO 25 mg orally twice daily and 306 patients receiving placebo during the 24-week double-blind treatment period.

The most commonly reported adverse reactions occurring in at least 3% of patients and more frequently than placebo included nasopharyngitis, bleeding-related events, headache, nausea, and abdominal pain. Nasopharyngitis was the most frequently observed adverse reaction, followed by bleeding events such as petechiae, contusion, epistaxis, ecchymosis, and gingival bleeding. Other reported bleeding manifestations included conjunctival bleeding, hematuria, purpura, hematoma, and intermenstrual bleeding.

Headache and migraine were commonly observed neurological adverse reactions, while gastrointestinal adverse reactions included nausea, abdominal discomfort, abdominal distension, upper abdominal pain, and generalized abdominal pain. Most adverse reactions were mild to moderate in severity.

Bleeding Reactions:

Bleeding reactions occurred in approximately 9% of patients treated with RHAPSIDO compared with 2% of patients receiving placebo during the 24-week placebo-controlled period. Petechiae and contusions were the most frequently reported bleeding events. No severe or life-threatening bleeding reactions were reported during clinical trials, and no association was observed between bleeding reactions and decreased platelet counts.[9]

7. Drug Interactions:

7.1 Effect of Other Drugs on RHAPSIDO:

RHAPSIDO is metabolized by CYP3A4. Concomitant use with strong or moderate CYP3A4 inhibitors should be avoided because these drugs can increase remibrutinib exposure and raise the risk of adverse reactions. Similarly, strong or moderate CYP3A4 inducers should also be avoided as they may decrease remibrutinib exposure and reduce therapeutic effectiveness.

7.2 Effect of RHAPSIDO on Other Drugs:

a. P-glycoprotein (P-gp) Substrates:

Remibrutinib acts as a P-gp inhibitor and may increase the exposure of P-gp substrate drugs such as digoxin. Patients receiving RHAPSIDO with P-gp substrates should be monitored closely for adverse reactions.

b. Antithrombotic Agents:

Caution is advised when RHAPSIDO is administered with antithrombotic or antiplatelet agents because of the increased risk of bleeding. Clinical studies did not allow concomitant use with anticoagulants. However, low-dose acetyl salicylic acid (up to 100 mg daily) and clopidogrel (up to 75 mg daily) were permitted during trials. Careful assessment of risks and benefits is recommended before combined use.[10]

8. Use in Specific Populations:

8.1 Pregnancy:

RHAPSIDO has limited available data regarding use during pregnancy, and the existing human data are insufficient to determine the risk of major birth defects, miscarriage, or adverse maternal and fetal outcomes associated with the drug. A pregnancy exposure registry has been established to monitor pregnancy outcomes in women exposed to RHAPSIDO during pregnancy. Healthcare providers and pregnant women are encouraged to report exposure to Novartis Pharmaceuticals Corporation.

Animal reproduction studies demonstrated developmental toxicity at high exposure levels. In pregnant rabbits, oral administration of remibrutinib during organogenesis produced fetal malformations including open or opaque eyes, small jaws, and hyperflexion of forelimbs, along with maternal toxicity at exposures significantly higher than the maximum recommended human dose (MRHD). In pregnant rats, no adverse fetal developmental effects were observed at exposure levels substantially greater than human exposure. Pre- and postnatal studies in rats showed maternal toxicity, prolonged gestation, and adverse effects on offspring survival at very high doses.

Because all pregnancies carry a background risk of birth defects, pregnancy loss, and other adverse outcomes, RHAPSIDO should only be used during pregnancy if the potential benefit justifies the possible risk to the fetus.

8.2 Lactation:

No information is available regarding the presence of remibrutinib in human milk, its effects on breastfed infants, or its influence on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's need for RHAPSIDO and any possible adverse effects on the breastfed child from the medication or the underlying maternal condition.

8.3 Pediatric Use:

The safety and effectiveness of RHAPSIDO have not been established in pediatric patients. Therefore, its use is not recommended in children or adolescents.

8.4 Geriatric Use:

Clinical studies included elderly patients between 65 and 85 years of age. No clinically meaningful differences in safety, tolerability, or therapeutic effectiveness were observed between geriatric patients and younger adults. However, caution should be exercised in elderly patients due to the potential presence of comorbid conditions and concomitant medications.[11]

8.5 Hepatic Impairment:

Remibrutinib exposure is increased in patients with mild, moderate, or severe hepatic impairment (Child-Pugh Classes A, B, and C). Increased systemic exposure may raise the risk of adverse reactions; therefore, the use of RHAPSIDO should be avoided in patients with any degree of hepatic impairment.[12]

9. CLINICAL PHARMACOLOGY:

9.1 Mechanism of Action:

Remibrutinib is an oral small-molecule kinase inhibitor that selectively inhibits Bruton's tyrosine kinase (BTK). BTK is an intracellular protein expressed in mast cells, basophils, B cells, macrophages, and thrombocytes. It plays an important role in intracellular signaling through Fc epsilon receptor-1 (FcεR1), Fc gamma receptors (FcγR), and the B-cell antigen receptor (BCR).

Remibrutinib also inhibits BTK-related kinases including TEC protein tyrosine kinase and BMX non-receptor tyrosine kinase. It suppresses mast cell and basophil degranulation, thereby reducing the release of histamine and other pro-inflammatory mediators triggered by pathogenic IgE or IgG antibodies directed against FcεR1 or IgE.[13]

9.2 Pharmacodynamics:

Exposure–Response:

Within the dose range of 0.2 to 4 times the recommended daily dose, a flat dose-response relationship was observed for the weekly urticaria activity score (UAS7) at Week 4.

Cardiac Electrophysiology:

At plasma concentrations approximately 9 times higher than the mean steady-state peak plasma concentrations achieved with the recommended dose, remibrutinib did not produce clinically significant QTc prolongation.

Effects on Blood Pressure:

The effect of remibrutinib on blood pressure was evaluated in patients with chronic spontaneous urticaria (CSU) using 24-hour ambulatory blood pressure monitoring (ABPM) at steady state (Week 4) compared with baseline in a multicenter, open-label study (A2305).

The study included 144 CSU patients inadequately controlled with H1 antihistamines who received remibrutinib 25 mg twice daily. Treatment with remibrutinib was not associated with clinically significant changes in blood pressure.[14]

9.3 Pharmacokinetics:

Following administration of remibrutinib 25 mg twice daily, the mean steady-state peak plasma concentration (Cmax) was 57 ng/mL and AUC was 193 ng·h/mL. Exposure increased dose-proportionally over the studied dose range. No clinically significant pharmacokinetic differences were observed between healthy subjects and patients with chronic spontaneous urticaria (CSU).

a. Absorption:

Remibrutinib reaches maximum plasma concentration (Tmax) approximately 1 hour after

administration. A high-fat meal did not produce clinically significant changes in drug exposure.

b. Distribution:

Remibrutinib is highly protein bound (95.4%) and has a large apparent volume of distribution of 1238 L.

Elimination

The estimated elimination half-life is 1–2 hours, with an apparent oral clearance of 160 L/hr.

c. Metabolism:

Remibrutinib is primarily metabolized by CYP3A4.

d. Excretion:

After intravenous administration of radiolabeled remibrutinib, approximately 70% of radioactivity was recovered in feces and 30% in urine, with very little unchanged drug excreted.

Specific Populations:

No clinically significant pharmacokinetic differences were observed based on age, sex, race, body weight, or renal impairment. However, hepatic impairment increased remibrutinib exposure, with higher AUC and Cmax observed in mild, moderate, and severe hepatic impairment.

Drug Interactions:

Strong CYP3A4 inhibitors such as ritonavir significantly increased remibrutinib exposure, while strong CYP3A4 inducers such as carbamazepine markedly decreased exposure. Remibrutinib also increased exposure of P-gp substrates like digoxin and BCRP substrates like rosuvastatin.

In Vitro Studies:

Remibrutinib is a CYP3A4 and P-gp substrate. It inhibits multiple CYP enzymes and transporter systems, including P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, and MATE1.[15]

10. Non Clinical Toxicology:

10.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Animal studies showed no evidence of carcinogenic effects with remibrutinib in mice and rats at exposures higher than the recommended human dose.

Remibrutinib was not found to be mutagenic or clastogenic in standard in vitro and in vivo genetic toxicity studies, including Ames and micronucleus assays.

Fertility studies in rats demonstrated no adverse effects on male or female fertility at exposures several times greater than the maximum recommended human dose (MRHD) of 25 mg twice daily.[16]

11. Clinical Studies:

The efficacy of RHAPSIDO was evaluated in two identical Phase 3 clinical trials, REMIX-1 and REMIX-2, in adult patients with chronic spontaneous urticaria (CSU) who remained symptomatic despite H1 antihistamine treatment.[17]

Both studies were randomized, double-blind, placebo-controlled, and conducted over 52 weeks. A total of 925 adult patients were enrolled. Patients received either RHAPSIDO 25 mg twice daily or placebo for 24 weeks, followed by a 28-week open-label treatment period.

Patient Characteristics:

Patients included in the studies had persistent itching and hives for at least 6 weeks with moderate to severe disease activity.

- Mean age: 42–45 years.
- Female patients: 65–68%.
- Many patients had severe CSU (UAS7 ≥28).
- Mean disease duration: 5–7 years.
- Around half had previous angioedema.
- About one-third had prior exposure to anti-IgE biologics.

Study Endpoints:

The primary endpoints were improvement from baseline in:

- Weekly Itch Severity Score (ISS7).

- Weekly Hive Severity Score (HSS7).

The key secondary endpoint was improvement in:

- Weekly Urticaria Activity Score (UAS7)

Additional endpoints included:

- Patients achieving UAS7 ≤6 (well-controlled disease).
- Patients achieving UAS7 = 0 (complete absence of itch and hives).

Results:

RHAPSIDO demonstrated statistically significant improvement compared with placebo in both studies.

At Week 12:

- ISS7 and HSS7 scores showed marked reduction in itch and hive severity.
- UAS7 scores significantly improved compared with placebo.
- About 47–50% of RHAPSIDO-treated patients achieved UAS7 ≤6.
- Around 28–31% achieved complete symptom resolution (UAS7 = 0).

Improvement was observed as early as Week 2 and continued up to Week 24. Benefits were consistent regardless of baseline IgE levels.

Conclusion:

RHAPSIDO effectively reduced itching, hives, and overall disease activity in adults with CSU inadequately controlled by antihistamines and showed rapid and sustained clinical benefit.[18]

12. Patient Counseling Information:

Administration Instructions:

Advise patients to take RHAPSIDO with or without food. The tablet should be swallowed whole with water and should not be split, crushed, or chewed.[19]

Risk of Bleeding:

Inform patients that RHAPSIDO may increase the risk of bleeding. Patients should immediately report any signs or symptoms of bleeding to their healthcare provider.

Patients should also inform their healthcare practitioner before any surgical or dental procedure, as RHAPSIDO may need to be interrupted for 3–7 days before surgery. Caution is advised when RHAPSIDO is used together with antithrombotic or blood-thinning medications because of the increased bleeding risk.[20]

Live Vaccines:

Advise patients to inform healthcare providers that they are receiving RHAPSIDO before vaccination. Live or live-attenuated vaccines should not be administered during treatment with RHAPSIDO.

Pregnancy:

Inform patients that a pregnancy exposure registry is available to monitor pregnancy outcomes in women exposed to RHAPSIDO during pregnancy.

CONCLUSION

RHAPSIDO (remibrutinib) is a novel oral Bruton's tyrosine kinase (BTK) inhibitor developed for the treatment of adults with chronic spontaneous urticaria (CSU) who remain symptomatic despite H1-antihistamine therapy. By selectively inhibiting BTK-mediated activation of mast cells and basophils, remibrutinib reduces the release of histamine and inflammatory mediators responsible for itching, wheals, and swelling associated with CSU. Its targeted mechanism of action provides rapid and sustained symptom control with convenient oral administration.

Clinical studies, including the Phase 3 REMIX-1 and REMIX-2 trials, demonstrated significant improvements in itch severity, hive severity, and overall urticaria activity scores compared with placebo. Many patients achieved well-controlled disease and complete symptom resolution, with benefits observed early during treatment and maintained over time. These findings highlight the effectiveness of RHAPSIDO in patients with difficult-to-control CSU.

The safety profile of RHAPSIDO was generally manageable, with most adverse reactions being mild

to moderate. Common adverse effects included nasopharyngitis, headache, nausea, abdominal discomfort, and bleeding-related events. Because of the potential risk of bleeding and drug interactions, careful monitoring and appropriate patient selection are important during therapy.

Overall, RHAPSIDO represents an important advancement in targeted therapy for chronic spontaneous urticaria. Its oral dosing, selective BTK inhibition, rapid onset of action, and sustained efficacy make it a promising therapeutic option for patients whose symptoms are inadequately controlled with conventional antihistamine treatment.

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HOW TO CITE: M. Prasada Rao*, Y. Narasimha Rao, S. Rajini, H. Siva Kumar Naik, Clinical Review Of RHAPSIDO (Remibrutinib) In Chronic Spontaneous Urticaria, Int. J. Sci. R. Tech., 2026, 3 (6), 248-254. https://doi.org/10.5281/zenodo.20537949