

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

218436Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RHAPSIDO safely and effectively. See full prescribing information for RHAPSIDO.

RHAPSIDO® (remibrutinib) tablets, for oral use
Initial U.S. Approval: 2025

INDICATIONS AND USAGE
RHAPSIDO® is a kinase inhibitor indicated for the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment. (1)

Limitations of Use: Not indicated for other forms of urticaria. (1)

DOSAGE AND ADMINISTRATION
Recommended dosage is 25 mg orally twice daily with or without food. (2.1)
• Swallow tablets whole. Do not split, crush, or chew RHAPSIDO. (2.1)
• Interrupt RHAPSIDO for 3 to 7 days pre- and post-surgery. (2.2)

DOSAGE FORMS AND STRENGTHS
Tablets: 25 mg (3)

CONTRAINDICATIONS
None. (4)

WARNINGS AND PRECAUTIONS
• **Risk of Bleeding:** Monitor for signs and symptoms of bleeding. Interrupt treatment with RHAPSIDO if bleeding is observed or pre- and post-surgery. Concomitant use of antithrombotic agents with RHAPSIDO may further increase risk of bleeding. (5.1)
• **Live Attenuated Vaccines:** Avoid live or live-attenuated vaccines in patients receiving RHAPSIDO. (5.2)

ADVERSE REACTIONS
The most common adverse reactions (incidence ≥3%) were nasopharyngitis, bleeding, headache, nausea and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
• Strong or Moderate CYP3A4 Inhibitors: Avoid concomitant use with RHAPSIDO. (7.1)
• Strong or Moderate CYP3A4 Inducers: Avoid concomitant use with RHAPSIDO. (7.1)
• P-gp Substrates: Exposure increases where minimal concentration changes may lead to serious adverse reactions: Monitor more frequently for adverse reactions when used concomitantly with RHAPSIDO. (7.2)
• Antithrombotic Agents: Consider the risks and benefits of concomitant use of antithrombotic agents with RHAPSIDO. (7.2)

USE IN SPECIFIC POPULATIONS
• Mild, Moderate, or Severe Hepatic Impairment: Avoid use of RHAPSIDO. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.
Revised: 9/2025

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FULL PRESCRIBING INFORMATION

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.

Limitations of Use:

RHAPSIDO is not indicated for other forms of urticaria.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage is 25 mg taken orally twice daily with or without food.

- Swallow RHAPSIDO tablet whole with water. Do not split, crush, or chew RHAPSIDO.

Missed Dose(s)

If a dose or doses of RHAPSIDO is missed, skip the missed dose, and take the next dose at its regularly scheduled time. Do not take an extra dose(s) of RHAPSIDO to make up for a missed dose(s).

2.2 Temporary Interruption of RHAPSIDO for Surgery

Interrupt treatment with RHAPSIDO for 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding [*see Warnings and Precautions (5.1), Adverse Reactions (6.1) and Drug Interactions (7.2)*].

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Bleeding

In placebo-controlled studies in patients with CSU, mucocutaneous-related bleeding occurred in 9% of patients who received RHAPSIDO [*see Adverse Reactions (6.1)*]. Interrupt treatment with RHAPSIDO if bleeding is observed and resume if the benefit is expected to outweigh the risk.

Interrupt treatment with RHAPSIDO for 3 to 7 days pre- and post-surgery or invasive procedures [*see Dosage and Administration (2.2)*].

Use of antithrombotic agents concomitantly with RHAPSIDO may further increase the risk of bleeding [*see Drug Interactions (7.2)*]. Consider the benefits and risks of antithrombotic agents when used concomitantly with RHAPSIDO.

Monitor for signs and symptoms of bleeding.

5.2 Live Attenuated Vaccines

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.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse drug reaction (ADR) rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of RHAPSIDO was based on a pooled safety population from two identical clinical trials of 52 weeks duration, REMIX-1 and REMIX-2 [see *Clinical Studies (14)*]. The pooled safety population consisted of 912 adult patients with CSU who remain symptomatic despite H1 antihistamine treatment and who received RHAPSIDO 25 mg orally twice daily (N=606) or placebo (N=306) for 24 weeks during the double-blind, controlled treatment period of the trial.

Adverse reactions that occurred at an incidence greater than or equal to 3% and more common than the placebo group from the pooled safety population (REMIX-1 and REMIX-2) during the 24-week blinded, placebo-controlled treatment period are shown in Table 1.

Table 1 Adverse Reactions with RHAPSIDO with Incidence $\geq$ 3% and More Common than Placebo in Adult Patients with CSU (REMIX-1 and REMIX-2)

Adverse Reaction	RHAPSIDO (N = 606) n (%)	Placebo (N = 306) n (%)
Nasopharyngitis ^a	67 (11%)	27 (9%)
Bleeding ^b	55 (9%)	6 (2%)
Headache ^c	41 (7%)	19 (6%)
Nausea	18 (3%)	5 (2%)
Abdominal Pain ^d	18 (3%)	6 (2%)

^a includes acute sinusitis, chronic sinusitis, nasopharyngitis, pharyngitis, pharyngitis streptococcal, rhinitis, rhinitis allergic, and upper respiratory tract infection

^b includes conjunctival bleeding, contusion, ecchymosis, epistaxis, gingival bleeding, hematoma, hematuria, hemorrhagic ovarian cyst, intermenstrual bleeding, petechiae, purpura, and urinary occult blood

^c includes headache and migraine

^d includes abdominal discomfort, abdominal distention, abdominal pain and abdominal pain upper

Specific Adverse Reactions

Bleeding

In the pooled safety population (REMIX-1 and REMIX-2), bleeding occurred in 9% of patients treated with RHAPSIDO compared to 2% in the placebo group during the 24-week controlled treatment period [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.1)*, and *Drug Interactions (7.2)*]. Petechiae (4%) and contusion (2%) were the most commonly reported reactions in patients treated with RHAPSIDO. No severe bleeding reactions occurred. No association between bleeding reactions and low platelet counts was observed. In patients treated with RHAPSIDO, 0.5% experienced bleeding reactions that led to RHAPSIDO discontinuation, while none of these reactions occurred in the placebo group. Similar safety findings were observed through Week 52 [see *Clinical Studies (14)*].

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on RHAPSIDO

Strong or Moderate CYP3A4 Inhibitors

Avoid use of RHAPSIDO with strong or moderate CYP3A4 inhibitors.

Remibrutinib is a CYP3A4 substrate. Concomitant use with a strong or moderate CYP3A4 inhibitor increases remibrutinib exposure [see *Clinical Pharmacology (12.3)*], which may increase the risk of RHAPSIDO adverse reactions.

Strong or Moderate CYP3A4 Inducers

Avoid use of RHAPSIDO with strong or moderate CYP3A4 inducers.

Remibrutinib is a CYP3A4 substrate. Concomitant use with a strong or moderate CYP3A4 inducer decreases remibrutinib exposure [see *Clinical Pharmacology (12.3)*], which may decrease the efficacy of RHAPSIDO.

7.2 Effect of RHAPSIDO on Other Drugs

P-gp Substrates

Monitor more frequently for adverse reactions when using RHAPSIDO with P-glycoprotein (P-gp) substrates where minimal concentration changes may lead to serious adverse reactions (e.g., digoxin).

Remibrutinib is a P-gp inhibitor. Remibrutinib increases exposure of P-gp substrates, which may increase the risk of adverse reactions related to P-gp substrates [see *Clinical Pharmacology* (12.3)].

Antithrombotic Agents

Consider the risks and benefits of concomitant administration of antithrombotic agents with RHAPSIDO [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.1), and *Adverse Reactions* (6.1)].

No data are available on concomitant use of RHAPSIDO with anticoagulants. The concomitant use of RHAPSIDO and anticoagulants was not allowed in clinical studies. Use of the antiplatelet agents, acetyl salicylic acid at doses up to 100 mg daily or clopidogrel up to 75 mg daily, was allowed in the RHAPSIDO clinical studies.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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.

Risk Summary

Available data on the use of RHAPSIDO during pregnancy are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes.

In animal reproduction studies, oral administration of remibrutinib to pregnant rabbits during organogenesis at exposures 141-times the human exposure at the maximum recommended human dose (MRHD) of 25 mg twice daily based on area under the curve (AUC) resulted in adverse developmental outcomes including external malformations. No adverse developmental effects were observed with oral administration of remibrutinib to pregnant rats during organogenesis at exposures up to 126-times the human exposure at the MRHD (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development (EFD) study in pregnant rabbits, remibrutinib was administered orally at doses of 100, 300, and 450 mg/kg/day during the period of organogenesis. Increased fetal external malformations (e.g. open/opaque eyes, small jaws, hyperflexion of forelimbs) and maternal toxicity (transiently reduced food consumption and adverse clinical signs) occurred at 300 mg/kg/day (141-times the MRHD based on AUC). The fetal findings were considered unlikely to be secondary to the maternal toxicity. The dose of 450 mg/kg/day was not tolerated by the pregnant rabbits.

In an EFD study in pregnant rats, remibrutinib was administered orally at doses of 100, 300, and 1000 mg/kg/day during the period of organogenesis. Remibrutinib did not cause adverse effects to the fetus at exposures up to 126 times that at the MRHD based on AUC.

In a pre- and postnatal development (PPND) study, remibrutinib was administered orally to pregnant rats at doses of 100, 300, and 1000 mg/kg/day from gestation day 6 to lactation day (LD) 21. Remibrutinib induced adverse effects at 1000 mg/kg/day (approximately 194 times the MRHD based on body surface area [BSA]), affected maternal animals (moribundity and clinical signs of toxicity, slightly longer gestation lengths) and offspring up to LD1 (slightly higher mean number of stillborn, dead, or missing pups, and smaller mean litter size). No adverse effects at doses up to 1000 mg/kg/day were noted in the surviving offspring developing into adulthood. No effects were observed at 300 mg/kg/day (approximately 58 times the MRHD based on BSA).

8.2 Lactation

Risk Summary

No data are available regarding the presence of remibrutinib in either human or animal milk, its effects on the breastfed child, or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RHAPSIDO and any potential adverse effects on the breastfed child from RHAPSIDO or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of RHAPSIDO have not been established in pediatric patients.

8.5 Geriatric Use

Of the total number of patients treated with RHAPSIDO in clinical studies for CSU, 53 (8.7%) were 65 to 85 years of age, with no patients over 85 years of age [see *Clinical Studies (14)*]. There were no observed differences in safety and/or effectiveness in geriatric patients compared to younger adult patients.

8.6 Hepatic Impairment

RHAPSIDO exposure is increased in patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, and C) relative to patients with normal hepatic function. Avoid use of RHAPSIDO in patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B, and C) [see *Clinical Pharmacology (12.3)*].

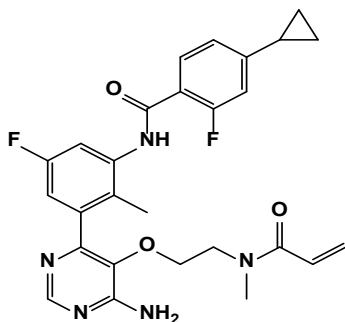
10 OVERDOSAGE

Consider contacting the poison help line (1-800-222-1222) or a medical toxicologist for overdose management recommendations.

11 DESCRIPTION

RHAPSIDO (remibrutinib) is a kinase inhibitor.

Its empirical formula (remibrutinib) is $C_{27}H_{27}F_2N_5O_3$. The chemical name for remibrutinib is N-(3-{6-Amino-5-[2-(N-methylprop-2-enamido)ethoxy]pyrimidin-4-yl}-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide. Its molecular weight is approximately 507.54 g/mol. The chemical structure of remibrutinib is:



Remibrutinib is white to pale yellow powder, and it is practically insoluble in water.

RHAPSIDO is supplied as film-coated tablets for oral administration, with each film-coated tablet containing 25 mg of remibrutinib. The tablet core inactive ingredients are copovidone, croscarmellose sodium, mannitol, microcrystalline cellulose, sodium lauryl sulfate, and sodium stearyl fumarate. The tablet coating inactive ingredients are polyethylene glycol 4000, polyvinyl alcohol, red iron oxide (E172), talc, titanium dioxide (E171), and yellow iron oxide (E172).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

12.2 Pharmacodynamics

Exposure-Response

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

Cardiac Electrophysiology

At concentrations approximately 9 times the mean steady state peak plasma concentrations provided by the recommended dose, clinically significant QTc prolongation was not observed.

Effects on Blood Pressure

The effect of remibrutinib treatment on blood pressure was assessed in CSU patients using a 24-hour blood pressure measurement by ambulatory blood pressure monitoring (ABPM) at steady state (Week 4) compared to baseline in a multicenter, open-label study (A2305). The study enrolled 144 patients with CSU inadequately controlled by H1 antihistamines, who were administered remibrutinib 25 mg twice daily. Remibrutinib 25 mg twice daily was not associated with clinically significant changes in blood pressure.

12.3 Pharmacokinetics

Following administration of remibrutinib 25 mg twice daily, the mean (standard deviation) C_{max} is 57 (27) ng/mL and AUC_{last} is 193 (136) ng·h/mL at steady state. Remibrutinib C_{max} and AUC increase in a dose-proportional manner between 0.4 to 4 times the recommended dosage. Following administration of multiple doses of 25 mg twice daily, C_{max} increases 1.6-fold and AUC_{0-4} increases 2.7-fold.

No clinically significant differences in remibrutinib pharmacokinetics were observed between healthy subjects and patients with CSU.

Absorption

Remibrutinib median (min, max) time to maximum plasma concentration (T_{max}) is 1 hour (0, 4 hours) at steady state.

Effect of food

No clinically significant differences in remibrutinib pharmacokinetics were observed following administration of a high-fat meal (1000 calories, 50% fat).

Distribution

Remibrutinib blood-to-plasma ratio is 0.813 in vitro. Plasma protein binding is 95.4% and is not concentration-dependent in vitro. The estimated remibrutinib steady state apparent (oral) volume of distribution is 1238 L.

Elimination

Remibrutinib estimated elimination half-life is 1 to 2 hours with an apparent (oral) clearance of 160 L/hr.

Metabolism

Remibrutinib is primarily metabolized by CYP3A4.

Excretion

Following IV administration of ^{14}C remibrutinib to healthy subjects, 70% of the total radioactivity was recovered in feces (0% as unchanged remibrutinib), and 30% was recovered in urine (2.9% as unchanged remibrutinib).

Specific Populations

No clinically significant differences in the pharmacokinetics of remibrutinib were observed based on age (range: 18 to 80 years), sex (63.5% females and 36.5% males), race/ethnicity (59.3% Non-Asian [White, Black, and Others], 8.8% Mainland Chinese, 12.2% Japanese, and 19.7% other Asian), body weight (range: 39 to 162 kg), and mild (eGFR 60-89 mL/min/1.73 m², estimated by Cockcroft-Gault), moderate (eGFR 30-59 mL/min/1.73 m²) or severe (eGFR 15-29 mL/min/1.73 m²) renal impairment.

Patients with Hepatic Impairment

The pharmacokinetics of remibrutinib were evaluated in subjects with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), and severe (Child-Pugh Class C) hepatic impairment following administration of 25 mg twice daily. Relative to patients with normal hepatic function, remibrutinib AUC increased 2.33-fold and $C_{\max}$ increased 1.85-fold in patients with mild hepatic impairment, AUC increased 2.3-fold and $C_{\max}$ increased 1.65-fold in patients with moderate hepatic impairment, and AUC increased 3.49-fold and $C_{\max}$ increased 1.99-fold in patients with severe hepatic impairment [see *Use in Special Populations* (8.6)].

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Strong CYP3A4 Inhibitors: Remibrutinib $C_{\max}$ increased by 3.3-fold and AUC increased by 4.3-fold following concomitant administration with ritonavir (a strong CYP3A4 inhibitor) 100 mg twice daily for 4 days [see *Drug Interactions* (7.1)].

Remibrutinib $C_{\max}$ increased by 1.24-fold and AUC increased by 1.3-fold when co-administered with grapefruit juice.

Moderate CYP3A4 Inhibitors: Remibrutinib $C_{\max}$ is predicted to increase by approximately 1.9-fold and AUC is predicted to increase by approximately 2.3-fold following concomitant administration with erythromycin (a moderate CYP3A4 inhibitor) 500 mg four times a day for 7 days [see *Drug Interactions* (7.1)].

Strong CYP3A4 Inducers: Remibrutinib $C_{\max}$ decreased by 74% and AUC decreased by approximately 77% following concomitant administration with carbamazepine (a strong CYP3A4 inducer) 300 mg twice daily for 14 days [see *Drug Interactions* (7.1)].

Moderate CYP3A4 Inducers: Remibrutinib $C_{\max}$ is predicted to decrease by approximately 60% and AUC is predicted to decrease by approximately 64% following concomitant administration with efavirenz (a moderate CYP3A4 inducer) 600 mg once daily for 14 days [see *Drug Interactions* (7.1)].

P-gp Substrates: Co-administration of remibrutinib at four times the recommended dosage with a single dose of 0.25 mg digoxin (a P-gp substrate) increased digoxin $C_{\max}$ by 2.1-fold and AUC by 1.4-fold [see *Drug Interactions* (7.1)].

BCRP Substrates: Co-administration of remibrutinib at four times the recommended dosage with a single dose of 10 mg rosuvastatin (a BCRP and OATP1B substrate) increased rosuvastatin $C_{\max}$ by 1.6-fold and AUC by 1.7-fold.

Other Drugs: No clinically significant differences in the pharmacokinetics of the following drugs were observed when used concomitantly with remibrutinib: oral midazolam (CYP3A4 substrate), oral contraceptives containing ethinyl estradiol and levonorgestrel (CYP3A4 substrate), tolbutamide (CYP2C9 substrate), caffeine (CYP1A2 substrate), and coproporphyrin I (an endogenous OATP1B substrate).

In Vitro Studies

CYP450 Enzymes: Remibrutinib is a CYP3A4 substrate. Remibrutinib inhibits CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5. Remibrutinib induces CYP1A2, CYP2B6, CYP2C9 and CYP3A4/5.

Transporter Systems: In vitro, remibrutinib is a P-gp substrate. Remibrutinib inhibits P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2 and MATE1.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Remibrutinib did not show evidence of carcinogenic potential in a 6-month rasH2 mouse study at oral doses up to 1500 mg/kg/day and a 2-year rat carcinogenicity study at oral doses up to 300 mg/kg/day (approximately 8 times and 98 times than MRHD of 25 mg twice daily based on AUC for males and females, respectively).

Remibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay and was not clastogenic in an in vitro micronucleus assay in human peripheral lymphocytes or in an in vivo blood reticulocyte micronucleus assay in rats.

In a fertility study in rats, remibrutinib did not impact fertility in female or male rats up to the maximum achievable exposures of 79 and 15 times higher than MRHD of 25 mg twice daily based on AUC.

14 CLINICAL STUDIES

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 ≥ 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 in a 2:1 ratio to receive either RHAPSIDO 25 mg or placebo, respectively, 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.

Demographics and baseline characteristics in REMIX-1 and REMIX-2 are provided in Table 2.

Table 2 Baseline Demographic and Disease Characteristics of Adult Patients with CSU in REMIX-1 and REMIX-2

	REMIX-1 (N=462)	REMIX-2 (N=450)
Age		
18-65 years, n (%)	419 (91)	416 (92)
>65 years, n (%)	43 (9)	34 (8)
Mean age, years	45	42
Sex, n (%)		
Female	313 (68)	294 (65)
Race, n (%)		
White or Caucasian	270 (58)	234 (52)
Black or African American	15 (3)	10 (2)
Asian	139 (30)	201 (45)
Ethnicity, n (%)		
Hispanic/Latino	116 (25)	21 (5)
Disease characteristics		
UAS7 ≥ 28 , n (%)	298 (65)	269 (60)
Mean HSS7 score	16	16
Mean ISS7 score	15	14
Previous experience of Angioedema, n (%)	240 (52)	208 (46)
Previous exposure to anti-IgE biologics, n (%)	147 (32)	138 (31)
CSU: chronic spontaneous urticaria, UAS7: weekly urticaria activity score, HSS7: weekly hive severity score, ISS7 score: weekly itch severity score		

The reported mean duration of CSU at enrollment across treatment groups was 6.6 and 5.2 years in REMIX-1 and REMIX-2, 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 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 REMIX-1 and REMIX-2 studies, the co-primary and all secondary endpoints showed statistically significant improvement in itch and hives symptoms in patients treated with RHAPSIDO compared to patients treated with placebo. Results are presented in Table 3.

Table 3 Efficacy Results of Adult Patients with CSU in REMIX-1 and REMIX-2 at Week 12^a

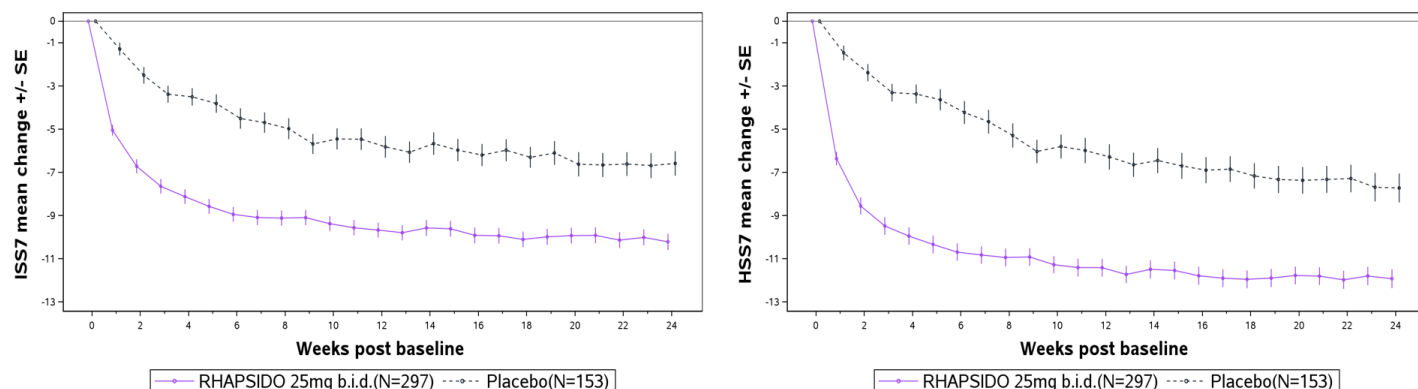
	REMIX-1		REMIX-2	
	RHAPSIDO (N = 309)	Placebo (N = 153)	RHAPSIDO (N = 297)	Placebo (N = 153)
Change from Baseline in ISS7 at Week 12				
LS mean (SE) CFB	-9.52 (0.34)	-6.89 (0.47)	-8.95 (0.34)	-5.72 (0.45)
Difference in LS mean (SE) vs placebo	-2.63 (0.54)		-3.23 (0.55)	
95% CI for difference	-3.70, -1.56		-4.29, -2.16	
Change from Baseline in HSS7 at Week 12				
LS mean (SE) CFB	-10.47 (0.40)	-6.86 (0.55)	-10.47 (0.39)	-6.00 (0.53)
Difference in LS mean (SE) vs placebo	-3.61 (0.64)		-4.47 (0.64)	
95% CI for difference	-4.85, -2.36		-5.71, -3.23	
Change from Baseline in UAS7 at Week 12				
LS mean (SE) CFB	-20.02 (0.72)	-13.79 (0.98)	-19.41 (0.70)	-11.73 (0.95)
Difference in LS mean (SE) vs placebo	-6.22 (1.14)		-7.68 (1.14)	
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 (30.0)	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	

LS Mean: Least squares mean, SE: standard error, CFB: change from baseline, CI: confidence interval

^a Multiple imputation techniques were implemented for missing data.

Figure 1 shows the effect of RHAPSIDO over time up to Week 24 in REMIX-2 patients treated with RHAPSIDO. The results were similar in REMIX-1.

Figure 1 Mean Change from Baseline in Weekly Itch Severity Score (ISS7) and Hive Severity Score (HSS7) up to Week 24 in REMIX-2 (Observed Data)



Improvements in ISS7 and HSS7 at Week 12 were consistent regardless of patients' baseline total IgE level.

16 HOW SUPPLIED/STORAGE AND HANDLING

RHAPSIDO tablets are supplied as described in Table 4:

Table 4 RHAPSIDO Tablets and Package Configuration

Strength	Tablet Description	Package Configuration	NDC
25 mg	light yellow, round, curved, unscored, film-coated tablet, debossed with "LV" on one side and Novartis logo on the other side. Tablet diameter is 7 mm.	40 mL HDPE bottle containing 60 tablets with 2 gm silica gel and a child-resistant closure	0078-1483-20

Storage

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) [see USP Controlled Room Temperature]. Dispense and store in the original container in order to protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information).

Administration Instructions:

Inform patients to take RHAPSIDO with or without food. Advise patients not to split, crush, or chew the tablet and to swallow the tablet whole with water [see *Dosage and Administration* (2.1)].

Risk of Bleeding:

Inform patients that bleeding can occur with the use of RHAPSIDO, and to report any signs and symptoms to their healthcare practitioner. Inform patients that RHAPSIDO should be interrupted for 3 to 7 days for any surgical procedures. Instruct patients to inform their healthcare practitioner if they use RHAPSIDO with antithrombotic agents due to the potential increased risk of bleeding [see *Dosage and Administration* (2.2) and *Warnings and Precautions* (5.1)].

Live Attenuated Vaccines:

Instruct patients to inform the healthcare practitioner that they are taking RHAPSIDO prior to any potential vaccinations. Advise patients that the vaccines containing live virus (live and live-attenuated) should not be given during treatment with RHAPSIDO [see *Warnings and Precautions* (5.2)].

Pregnancy:

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to RHAPSIDO during pregnancy [*see Use in Specific Populations (8.1)*].

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Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936

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T202X-XX

Patient Information
RHAPSIDO® (RAP-si-doe)
(remibrutinib)
tablets, for oral use

What is RHAPSIDO?

RHAPSIDO is a prescription medicine used to treat adults with chronic spontaneous urticaria (CSU) who continue to have symptoms that are not controlled with antihistamine treatment.

RHAPSIDO should not be used to treat any other forms of hives (urticaria).

It is not known if RHAPSIDO is safe and effective in children.

Before taking RHAPSIDO, tell your healthcare provider about all of your medical conditions, including if you:

- have had a recent surgery or plan to have surgery. Your healthcare provider may tell you to stop taking RHAPSIDO for at least 3 to 7 days before and after any planned medical or surgical procedures.
- have bleeding problems or are taking a blood thinner medicine.
- have liver problems.
- are pregnant or plan to become pregnant. It is not known if RHAPSIDO will harm your unborn baby.
Pregnancy Exposure Registry: If you become pregnant during treatment with RHAPSIDO, talk to your healthcare provider about registering in the pregnancy exposure registry for RHAPSIDO. You or your healthcare provider can enroll in this registry by calling 1-888-669-6682. The purpose of this registry is to collect information about the safety of RHAPSIDO during pregnancy.
- are breastfeeding or plan to breastfeed. It is not known if RHAPSIDO passes into your breast milk. You and your healthcare provider should decide the best way to feed your baby while taking RHAPSIDO.
- have recently received or are scheduled to receive an immunization (vaccine). Talk to your healthcare provider about receiving any immunizations before taking RHAPSIDO. You should not receive live or live-attenuated vaccines during treatment with RHAPSIDO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking RHAPSIDO with certain other medicines may affect how RHAPSIDO works, or it may affect how other medicines work and can cause side effects.

How should I take RHAPSIDO?

- Take RHAPSIDO exactly as your healthcare provider tells you to take it.
- Do not change your dose or stop taking RHAPSIDO unless your healthcare provider tells you to.
- Take 1 RHAPSIDO tablet 2 times a day.
- RHAPSIDO can be taken with or without food.
- Swallow RHAPSIDO tablet whole with water. **Do not** split, crush, or chew the tablets.
- If you miss a dose of RHAPSIDO, skip the missed dose, and take the next dose at your regular time. **Do not** take an extra dose of RHAPSIDO to make up for a missed dose.
- If you take too much RHAPSIDO, call your healthcare provider or Poison Help line at 1-800-222-1222, or go to the nearest hospital emergency room right away.

What are possible side effects of RHAPSIDO?

RHAPSIDO may cause serious side effects, including:

Risk of bleeding. Bleeding may happen while being treated with RHAPSIDO. Your healthcare provider will monitor you for signs and symptoms of bleeding and may stop your treatment if bleeding happens. Your risk of bleeding may increase if you are also taking a blood thinner medicine. Tell your healthcare provider right away if you get any signs or symptoms of bleeding, such as:

- bruising, or red or purple skin marks
- pink or brown urine
- headache, dizziness, confusion, or feeling weak
- red or black stools that look like tar

The most common side effects with RHAPSIDO may include nasal congestion, sore throat, and runny nose (nasopharyngitis), bleeding, headache, nausea, abdominal pain.

These are not all the possible side effects of RHAPSIDO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store RHAPSIDO?

- Store RHAPSIDO at room temperature between 68°F to 77°F (20°C to 25°C).
- Store RHAPSIDO in the original container to protect from moisture.

Keep RHAPSIDO and all medicines out of the reach of children.

General information about the safe and effective use of RHAPSIDO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. **Do not** use RHAPSIDO for a condition for which it is not prescribed. **Do not** give RHAPSIDO to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about RHAPSIDO that is written for health professionals.

What are the ingredients in RHAPSIDO?

- Active Ingredient: remibrutinib
- Inactive Ingredients: copovidone, croscarmellose sodium, mannitol, microcrystalline cellulose, sodium lauryl sulfate, and sodium stearyl fumarate. The tablet coating is composed of polyethylene glycol 4000, polyvinyl alcohol, red iron oxide (E172), talc, titanium dioxide (E171), and yellow iron oxide (E172).

Distributed by:

Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936
For more information, go to www.RHAPSIDO.com or call 1-888-669-6682.

This Patient Information has been approved by the U.S. Food and Drug Administration

Issued: 9/2025

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FRONT PANEL



00781 48320 8

NDC 0078-1483-20

Rhapsido[®]
(remibrutinib) tablets

25 mg per tablet

Swallow tablets whole with water.
Do not split, crush, or chew tablets.
Rx only 60 tablets

3  NOVARTIS 300128433 US

Dispense and store in original container at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F). Protect from moisture.

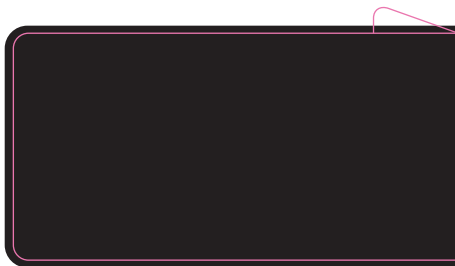


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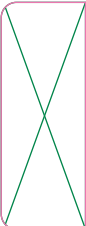


Peel Here

BACKSIDE OF FRONT LABEL



BACK LABEL



Rhapsido[®]
(remibrutinib) tablets

25 mg per tablet

Swallow tablets whole with water. Do not split, crush, or chew tablets.
Recommended Dosage: See Prescribing Information.
Each tablet contains 25 mg remibrutinib.
Keep out of reach of children.

For more information, visit www.Rhapsido.com or call 1-888-669-6682.

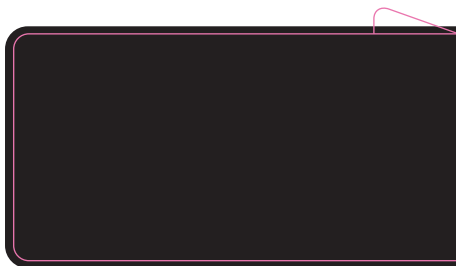
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Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936
Product of China © Novartis

NDC 0078-1483-20

FRONT PANEL



BACKSIDE OF FRONT LABEL



BACK LABEL



Professional Courtesy Package - Not for Sale

15-Day Supply
30 tablets

25 mg
per
tablet

(remibrutinib) tablets



Information on
patient support here



SCAN the QR code with your smartphone
or visit www.support.RHAPSIDO.com

Manufactured by:
Novartis d.o.o., Ljubljana, 1000, Slovenia for
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936
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Product of China
300129702-US

Rhapsido
(remibrutinib) tablets

25 mg per
tablet

Swallow tablets whole with
water. Do not split, crush, or
chew tablets.

Each tablet contains 25 mg
remibrutinib.

Recommended Dosage:
See Prescribing Information.

Not for Sale
Professional Courtesy Package

NDC 0078-1483-93
Rx only

Rhapsido
(remibrutinib) tablets

25 mg per
tablet

15-Day Supply
30 tablets

Professional Courtesy Package - Not for Sale

NOVARTIS

LOT XXXXXX
EXP YYYY-MMM-DD

Rhapsido
(remibrutinib) tablets

25 mg per
tablet

Dispense and store in original
container at 20°C to 25°C
(68°F to 77°F); excursions
permitted between 15°C and
30°C (59°F and 86°F) [see USP
Controlled Room Temperature].
Protect from moisture.

Keep out of reach of children.

Not for Sale
Professional Courtesy Package

LOT XXXXXX
EXP YYYY-MMM-DD



Professional Courtesy Package - Not for Sale

Rhapsido
(remibrutinib) tablets

25 mg per tablet

Rx only 30-Day Supply
60 tablets (2 sample bottles each containing 30 tablets)

NDC 0078-1483-92

Information on
patient support here



SCAN the QR code
with your smartphone
or visit
www.support.RHAPSIDO.com

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Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936

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Product of China
300129181-US

Rhapsido
(remibrutinib) tablets

25 mg per tablet

Swallow tablets whole with water.
Do not split, crush, or chew tablets.

Each tablet contains 25 mg
remibrutinib.

Recommended Dosage:
See Prescribing Information.

Not for Sale
Professional Courtesy Package

Rhapsido
(remibrutinib) tablets

25 mg per tablet

Rx only 30-Day Supply
60 tablets (2 sample bottles each containing 30 tablets)

Professional Courtesy Package - Not for Sale

NOVARTIS

Rhapsido
(remibrutinib) tablets

25 mg per tablet

Dispense and store in original
container at 20°C to 25°C (68°F to
77°F); excursions permitted between
15°C and 30°C (59°F and 86°F) [see
USP Controlled Room Temperature].
Protect from moisture.

Keep out of reach of children.

Not for Sale
Professional Courtesy Package

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/s/

KATHLEEN M DONOHUE
09/30/2025 12:05:06 PM