Product Monograph

Including Patient Medication Information

[Pr]RHAPSIDO®

remibrutinib tablets

For oral use

25 mg of remibrutinib per tablet

Bruton's tyrosine kinase inhibitor

Novartis Pharmaceuticals Canada Inc.

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Date of Authorization:
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Part 1: Healthcare Professional Information

1. Indications

RHAPSIDO (remibrutinib tablets) is indicated for:

- the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment.

1.1. Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of RHAPSIDO in pediatric patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics

Geriatrics (≥ 65 years of age): RHAPSIDO may be administered to patients aged 65 years and over. Limited evidence from clinical studies suggests that use in the geriatric population is not associated with differences in safety or effectiveness.

2. Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6 Dosage Forms, Strengths, Composition, and Packaging).

4. Dosage and Administration

4.1. Dosing Considerations

Dose interruption

It is recommended to interrupt treatment with RHAPSIDO for 3 to 7 days before surgery and for 3 to 7 days after surgery, depending upon the type of surgery and the risk of bleeding (see sections 8 Adverse Reactions and 9 Drug Interactions).

4.2. Recommended Dose and Dosage Adjustment

The recommended dose of RHAPSIDO is 25 mg taken orally twice daily.

Special populations

Renal impairment: No dose adjustment of RHAPSIDO is required in patients with renal impairment. Elimination of unchanged remibrutinib via the kidney is minimal. There are limited data available in patients with severe renal impairment (see section 10.3 Pharmacokinetics).

Hepatic impairment: No dose adjustment of RHAPSIDO is required for patients with mild or moderate hepatic impairment. Remibrutinib exposure is increased in patients with hepatic impairment relative to patients with normal hepatic function (see section 10 Clinical Pharmacology). RHAPSIDO should be used with caution in patients with moderate hepatic impairment and avoided in patients with severe hepatic impairment (see 7 Warnings and Precautions, Hematologic).

Pediatric patients (below 18 years): The safety and efficacy of RHAPSIDO in pediatric patients have not been established.

4.4. Administration

RHAPSIDO is administered orally. RHAPSIDO can be taken with or without food. Patients should be instructed to swallow the tablet whole with water. RHAPSIDO should not be split, crushed, or chewed.

4.5. Missed Dose

If a patient misses a dose or doses of RHAPSIDO, the patient should be instructed to take the next dose at its regularly scheduled time. Extra doses of RHAPSIDO should not be taken to make up for the missed dose or doses.

5. Overdose

There was no experience with overdose in the pivotal Phase III clinical studies with RHAPSIDO. Doses up to 600 mg per day were well tolerated in the Phase I clinical studies with no evidence of dose-limiting adverse events.

In the event of an overdose, the patient should be treated symptomatically, and supportive measures should be instituted as required.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
oral	Tablet, 25 mg remibrutinib	Tablet core: copovidone, croscarmellose sodium, mannitol, microcrystalline cellulose, sodium lauryl sulfate, sodium stearyl fumarate.

		Tablet coating: polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172).

Description

25 mg tablets: light yellow, round, curved, unscored tablet with diameter 7 mm, debossed with “LV” on one side and “Novartis” Logo on the other side.

RHAPSIDO is supplied in PA/AL/PVC blister packs.

The following pack size is available:

- Packs containing 60 tablets (6 x 10).

7. Warnings and Precautions

Hematologic

- **Risk of bleeding**

In placebo-controlled Phase III studies, mild to moderate mucocutaneous bleeding events occurred in patients treated with RHAPSIDO. The most frequently reported events were bruising-related, such as petechiae and contusion (see 8 Adverse Reactions).

Instruct patients to seek medical advice if signs and symptoms suggestive of significant bleeding occur. If significant bleeding is suspected, interrupt RHAPSIDO 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.

- **Antithrombotic agents**

No data are available on co- administration of RHAPSIDO with anticoagulants. Co-administration of RHAPSIDO with anticoagulants was not allowed in clinical studies. Use of antiplatelet agents, acetylsalicylic acid (up to 100 mg daily) or clopidogrel (up to 75 mg daily) was allowed in the RHAPSIDO clinical studies. The risks and benefits of co-administration of antithrombotic agents with RHAPSIDO must be considered (see sections 4 Dosage and Administration and 8 Adverse Reactions).

Immune

- **Immune response to vaccines**

No data are available on the effects of live or live-attenuated vaccines in patients receiving RHAPSIDO; these vaccines should not be administered during treatment with RHAPSIDO.

Non-live vaccines can be given during RHAPSIDO treatment. To optimize the immune response with non-live vaccines, benefit-risk of treatment interruption of RHAPSIDO (1 week prior to a planned vaccination until 2 weeks after the vaccination) should be considered (see section 10 Clinical Pharmacology).

Reproductive Health

Sexually active females of reproductive potential must use effective contraception (methods that result in less than 1% pregnancy rates) during RHAPSIDO treatment and for at least 1 week after the last dose. Females of reproductive potential should be advised that animal studies have shown remibrutinib to be harmful to the developing fetus.

- **Fertility**

  There is no data on the effect of RHAPSIDO on human fertility. In a fertility study in rats, remibrutinib did not impact fertility in female or male rats at doses up to 1000 mg/kg/day. Maximum achievable exposure of remibrutinib was observed at 300 mg/kg/day which is equivalent to 79 times for females and 15 times for males the MRHD of 25 mg twice daily based on AUC.

7.1. Special Populations

7.1.1. Pregnancy

There are no adequate and well-controlled studies in pregnant women to inform a RHAPSIDO-associated risk. Based on findings in animal studies, advise patients that remibrutinib may cause fetal harm when RHAPSIDO is administered during pregnancy or if the patient becomes pregnant while taking RHAPSIDO.

In an embryo-fetal development study, oral administration of remibrutinib in rabbits during organogenesis induced teratogenicity and maternal toxicity. Increased incidences of open/opaque eyes, small jaws, and hyperflexion of the forelimbs were observed in rabbits following prenatal exposure to remibrutinib at 141 times the maximum recommended human dose (MRHD) of 25 mg twice daily based on area under curve (AUC), with a no observed adverse effect level (NOAEL) based safety margin of 23 times. The fetal findings were considered unlikely to be secondary to maternal toxicity. In an embryofetal development study in pregnant rats, no adverse effects were observed up to the highest tested dose of 1000 mg/kg/day, which is equivalent to 126 times the MRHD based on AUC (see section 16 Non-Clinical Toxicology).

7.1.2. Breastfeeding

It is unknown whether RHAPSIDO or its metabolites are transferred into human milk. There are no data on the effects of remibrutinib or its metabolites on the breastfed child or on milk production. Because of the potential for adverse drug reactions in the breastfed child, advise women not to breastfeed during treatment with RHAPSIDO and for 1 week after the last dose.

7.1.3. Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of RHAPSIDO in pediatric patients below 18 years of age have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4. Geriatrics

RHAPSIDO may be administered to patients aged 65 years and over. Limited evidence from clinical studies suggests that use in the geriatric population is not associated with differences in safety or effectiveness.

8. Adverse Reactions

8.1. Adverse Reaction Overview

The safety profile of RHAPSIDO is based on the pooled data set (N=912) of two Phase III studies, REMIX-1 and REMIX-2 in adult patients with CSU. Patients were treated with RHAPSIDO 25 mg twice daily (N=606) or placebo (N=306) for 24 weeks during the double-blind treatment period and continued in a 28-week open-label treatment period where all patients received RHAPSIDO 25 mg twice daily.

During the double-blind placebo-controlled period of the Phase III studies in adult patients with CSU, the most frequently reported adverse drug reaction (ADR) with RHAPSIDO (reported at a frequency ≥5%) was upper respiratory tract infections (14.7%). The severity of all the ADRs in these clinical studies was mild to moderate.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

The data described below reflect the exposure in adult patients with CSU who received RHAPSIDO 25mg twice daily (n = 606) or placebo (n=306) in REMIX-1 and REMIX-2 for 24 weeks at the recommended dosing regimens for 24 weeks.

Table 2 – Adverse drug reactions in patients with CSU at Week 24 (N=912) in pooled REMIX-1 and REMIX-2 clinical studies

Adverse drug reactions	**RHAPSIDO 25 mg twice daily N = 606 n (%)**	**Placebo N = 306 n (%)**
Upper respiratory tract infections[1]	89 (14.7%)	36 (11.8%)
Bleeding[2]	55 (9.1%)	6 (2.0%)
Headache[3]	41 (7%)	19 (6)
Nausea	18 (3%)	5 (2%)
Abdominal Pain[4]	18 (3%)	6 (2%)

Adverse drug reactions	RHAPSIDO 25 mg twice daily N = 606 n (%)	Placebo N = 306 n (%)
1)Includes upper respiratory tract infection, acute sinusitis, chronic sinusitis, H1N1 influenza, influenza, laryngitis, nasopharyngitis, pharyngitis, pharyngitis streptococcal, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, tonsillitis bacterial, upper respiratory tract infection bacterial, upper respiratory tract infection viral. 2)Includes conjunctival bleeding, contusion, ecchymosis, epistaxis, gingival bleeding, hematoma, hematuria, hemorrhagic ovarian cyst, intermenstrual bleeding, petechiae, purpura, and urinary occult blood 3)Includes headache and migraine. 4)Includes abdominal discomfort, abdominal distention, abdominal pain and abdominal pain upper.		

The safety profile of RHAPSIDO in patients treated for up to 52 weeks remained consistent with that observed up to 24 weeks in the pooled REMIX-1 and REMIX-2 studies.

Description of selected adverse drug reactions

Mucocutaneous bleeding events

In the 24-week placebo-controlled double-blind treatment period of the pooled REMIX-1 and REMIX-2 Phase III studies, mucocutaneous bleeding events occurred in 9.1% of patients treated with RHAPSIDO compared to 2.0% in the placebo group. The most common events were petechiae (3.8%) and contusion (2.3%). In patients treated with RHAPSIDO, 88.4% of these events were mild and 11.6% were moderate in severity, compared to 66.7% and 33.3% in the placebo group, respectively; none were severe. No association between mucocutaneous bleeding events and low platelet counts was observed. In patients treated with RHAPSIDO, 0.5% (3/606) experienced mucocutaneous bleeding events that led to RHAPSIDO discontinuation and 1.3% (8/606) experienced events that led to RHAPSIDO interruption, while none of these events occurred in the placebo group (see sections 4 Dosage and Administration and 9 Drug Interactions).

During the entire study period of up to 52 weeks, mucocutaneous bleeding events occurred in 9.2% of patients treated with RHAPSIDO. The severity of the mucocutaneous bleeding events up to 52 weeks were mild and moderate; none were severe. No additional RHAPSIDO interruptions and only one treatment discontinuation was reported with RHAPSIDO after the 24-week placebo-controlled double-blind treatment period.

9. Drug Interactions

9.2. Drug Interactions Overview

Effect of other drugs on RHAPSIDO

CYP3A4 inhibitors

Caution is required when using RHAPSIDO with strong CYP3A4 inhibitors. Co- administration of ritonavir, a strong CYP3A4 inhibitor, led to a 4.3- fold increase in the area under the curve (AUC) and a 3.3- fold increase in the C_{max} of remibrutinib.

No clinically relevant effect is expected with co-administration of moderate CYP3A4 inhibitors during RHAPSIDO treatment. Grapefruit juice, a moderate to strong inhibitor of intestinal CYP3A4, led to a minor 1.29-fold increase in AUC and a 1.24-fold increase in C_{max} of remibrutinib.

CYP3A4 inducers

Avoid co-administration of RHAPSIDO with strong or moderate CYP3A4 inducers. Co-administration of carbamazepine (strong to moderate CYP3A4 inducer) decreased the remibrutinib blood exposure by 74% (C_{max}) and 77% (AUC).

Effect of RHAPSIDO on other drugs

P-gp or BCRP substrates

Caution is required when using RHAPSIDO with P-gp substrates with a narrow therapeutic index such as digoxin, as this led to a 1.4-fold increase in AUC and a 2.1-fold increase in the C_{max} of digoxin.

Caution is required when using RHAPSIDO with breast cancer resistance protein (BCRP) substrates with a narrow therapeutic index. Co-administration of rosuvastatin (a BCRP substrate without a narrow therapeutic index) and remibrutinib led to a 1.7-fold increase in AUC and a 1.6-fold increase in C_{max} of rosuvastatin.

Oral contraceptives

Co-administration of RHAPSIDO is not expected to have an adverse impact on the efficacy of oral contraceptives containing ethinylestradiol and levonorgestrel (CYP3A4 substrates) as their exposure was not decreased in the presence of remibrutinib (1.28 and 1.36-fold increase in C_{max} and 1.16 and 1.39-fold increase in AUC, respectively).

9.4. Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 – Established or Potential Drug-Drug Interactions

Non-proprietary name(s) of the drug product(s)	Source of evidence	Effect	Clinical comment
Effect of other drugs on RHAPSIDO			
CYP3A4 inhibitors (e.g. ritonavir)	CT	Remibrutinib is predominately metabolized by CYP3A4 but is not considered a sensitive CYP3A4 substrate, since the AUC ratio is < 5-fold in the presence of strong CYP3A4 inhibitors.	Caution is required when using RHAPSIDO with strong CYP3A4 inhibitors. No clinically relevant effect is expected with co-administration of moderate CYP3A4 inhibitors during RHAPSIDO treatment.

CYP3A4 inducers (e.g. carbamazepine)	CT	The concomitant use of strong CYP3A4 inducers with remibrutinib is expected to result in decreased remibrutinib blood exposure.	Avoid co-administration of RHAPSIDO with strong or moderate CYP3A4 inducers.
Effect of RHAPSIDO on other drugs			
P-gp or BCRP substrates (e.g. digoxin, rosuvastatin)	CT	Remibrutinib inhibits P-gp and BCRP thus, remibrutinib may result in increased exposure to BCRP or Pg-p substrates.	Caution is required when using RHAPSIDO with P-gp substrates with a narrow therapeutic index. Caution is required when using RHAPSIDO with breast cancer resistance protein (BCRP) substrates with a narrow therapeutic index.
Oral contraceptives	CT	Co-administration of RHAPSIDO is not expected to have an adverse impact on the efficacy of oral contraceptives containing ethinylestradiol and levonorgestrel (CYP3A4 substrates) as their exposure was not decreased in the presence of remibrutinib.	Oral contraceptives can be administered with RHAPSIDO without the risk of losing efficacy.

Legend: CT = Clinical Trial

***In vitro* evaluation of drug interaction potential**

In vitro, remibrutinib was characterized as a weak reversible inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5, a time-dependent inhibitor of CYP3A4/5 and an inducer of CYP1A2, CYP2B6, CYP2C9 and CYP3A4/5.

In vitro, remibrutinib was characterized as an inhibitor of P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2 and MATE1.

In vitro data showed that remibrutinib is a P-gp substrate. The *in vitro* CYP metabolism is predominantly driven by CYP3A4.

9.5. Drug-Food Interactions

Under steady-state conditions in healthy subjects, co-administration of remibrutinib with a high-fat, high-calorie meal resulted in a 33% increase in AUC and no impact on the C_{max} of remibrutinib relative to fasted conditions. RHAPSIDO can be taken with or without food.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

Bruton's tyrosine kinase (BTK) is an intracellular protein selectively expressed in mast cells, basophils, B cells, macrophages and thrombocytes. BTK is a key node of the intracellular signaling via Fc epsilon receptor-1 (FcεRI), Fc gamma receptors (FcγR) and the B cell antigen receptor (BCR).

Remibrutinib is an oral, highly selective BTK inhibitor. It inhibits mast cell and basophil degranulation mediated by pathogenic IgE, and/or by IgG directed against the FcεRI or IgE, that produce FcεRI activation. In patients with CSU, remibrutinib prevents the release of histamine and other proinflammatory mediators that cause itch, hives, or angioedema.

Remibrutinib has a >200-fold selectivity for BTK relative to the BTK-related kinases tec protein tyrosine kinase (TEC) and BMX non-receptor tyrosine kinase (BMX); however some inhibition of these related kinases with the clinical use of RHAPSIDO cannot be excluded.

10.2. Pharmacodynamics

Clinical pharmacokinetic and pharmacodynamic (PK/PD) data estimated a BTK occupancy ≥96% in blood maintained throughout the entire day with remibrutinib 25 mg twice daily; this estimate is extrapolated from data obtained with a different formulation and dosing regimen than the recommended dose.

Immunoglobulins

As mature plasma cells are the main source of IgG and as they do not express BTK, an effect of remibrutinib on total levels of circulating IgG is not expected.

In the 24-week double-blind placebo-controlled treatment period of the pooled REMIX-1 and REMIX-2 Phase III studies, the mean change from baseline to minimum post-baseline value for IgG levels in remibrutinib was -0.80 g/L for remibrutinib and -0.59 g/L for placebo; the mean change from baseline to minimum post-baseline value for IgM levels was -0.22 g/L for remibrutinib and 0.08 g/L for placebo during the controlled period. The mean values of both IgG and IgM remained within the normal reference range in both arms and continued throughout the 52 weeks.

Cardiac electrophysiology

The effects of remibrutinib on QTc interval prolongation were predicted using concentration-QTc analysis. The upper bound of the 90% confidence interval for the predicted mean change in QTcF was below 10 msec at the expected C_{max} at supratherapeutic exposures. Therefore, no clinically significant prolongation of QTcF interval is expected with therapeutic dosing of remibrutinib.

Effect 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 at steady state (Week 4) compared to baseline in a multi-center, open-label study. 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.

10.3. Pharmacokinetics

The PK of remibrutinib at steady state was approximately linear in the total daily dose range of 10 to 200 mg, with no evidence of time and concentration dependency. Steady state is achieved as soon as after 2 to 3 days of treatment, with minor accumulation (<1.5-fold for doses below 100 mg b.i.d.). Based on population PK modeling, following administration of remibrutinib 25 mg twice daily, the mean (standard deviation) C_{max} is 57 (27) ng/mL and AUC_{tau} is 193 (136) ng*h/mL at steady state.

Absorption

Remibrutinib is rapidly absorbed and reaches C_{max} in the blood around 1-hour post-dose across all doses studied (0.5 mg to 600 mg). Absorption is considered to be almost complete. The absolute oral bioavailability is 33.8%.

Effect of food

Under steady-state conditions in healthy subjects, co-administration of remibrutinib with a high-fat, high-calorie meal resulted in a 33% increase in AUC and no impact on the C_{max} of remibrutinib relative to fasted conditions. RHAPSIDO may be taken with or without food.

Distribution

Remibrutinib is readily distributed to blood cells with a blood-to-plasma ratio of 0.813. Plasma protein binding amounts to 95.4% with no concentration dependence. Based on pooled data from population PK analysis, the volume of distribution at steady state was 58 liters (central compartment) and 1180 liters (peripheral compartment).

Metabolism

Remibrutinib is metabolized primarily by CYP3A4, leading to the formation of 18 inactive metabolites, all in low amounts in circulation. Remibrutinib was more abundant than the related compounds in blood (16.7%) after oral dosing.

Elimination

Remibrutinib had a mean elimination half-life ranging between 1 and 2 hours at steady state. Following IV administration of [^{14}C] remibrutinib, excretion of radioactivity (remibrutinib and metabolites) was approximately 70% of the administered dose in feces and 30% in urine. Renal excretion of unchanged remibrutinib after oral administration was minimal.

Special populations and conditions

A population PK (pop-PK) analysis conducted on remibrutinib data from 1152 patients showed that there was no clinically relevant effect in the PK of remibrutinib based on age (18 to 80 years), sex (63.5% females and 36.5% males), race/ethnicity (59.3% Non-Asian, 8.8% Mainland Chinese, 12.2% Japanese, and 19.7% Other Asian) and body weight (range 39 to 162 kg).

- **Geriatrics:** Of the 912 patients with CSU in the pivotal clinical studies, a total of 77 (8.4%) patients were 65 to 85 years of age, with no patients over 85 years of age. Based on pop-PK analysis in the clinical studies, no significant differences in the PK of remibrutinib were observed in patients ≥65 years of age versus younger adult patients.
- **Ethnic origin:** Based on the data from clinical studies (including REMIX-1 and REMIX-2 Phase III studies), as well as pop-PK and exposure-response analyses), race/ethnicity had no clinically relevant effect on remibrutinib PK. Therefore, no dose adjustment is required.
- **Hepatic Insufficiency:** The C_{max} and AUC of remibrutinib at steady state increased 1.85-fold and 2.15-fold in subjects with mild hepatic impairment (Child-Pugh class A), 1.65-fold and 2.07-fold in subjects with moderate hepatic impairment (Child-Pugh class B), and 1.99-fold and 3.12-fold in subjects with severe hepatic impairment (Child-Pugh class C), respectively, relative to subjects with normal hepatic function following an oral dose of 25 mg remibrutinib twice daily. There was no change in protein binding of remibrutinib in subjects with hepatic impairment as compared to subjects with normal hepatic function.
- **Renal Insufficiency:** Following an oral dose of 25 mg remibrutinib twice daily, the pop-PK analysis in patients with mild or moderate renal impairment and PK modeling data in patients with severe renal impairment revealed no clinically relevant differences in the PK of remibrutinib in patients with mild (estimated glomerular filtration rate (eGFR) 60 to <90 mL/min/1.73 m2), moderate (eGFR 45 to <60 mL/min/1.73 m2) or severe (eGFR 15 to <45 mL/min/1.73 m2) renal impairment when compared to patients with normal renal function.
- **Vaccination immune response study:** In a placebo-controlled study in healthy volunteers using remibrutinib 100 mg twice daily, the immune response to non-live vaccines was not significantly impacted when remibrutinib was interrupted for 1 week before until 2 weeks after vaccination. However, in comparison to placebo, concomitant remibrutinib treatment was associated with a 60% reduction of responders to the T cell-independent polysaccharide PPV23 vaccine. With T cell-dependent vaccines, smaller differences compared to placebo were observed. There was a 21% reduction in IgG response to keyhole limpet haemocyanin (KLH) vaccine (T cell-dependent neoantigen) as well as comparable response rates (1 to 14% reduction) for 3 out of 4 of the antigens in influenza vaccine (T cell-dependent) and a slightly more pronounced reduction (27%) for 1 out of 4 of the influenza antigens.

11. Storage, Stability, and Disposal

Do not store above 30°C.

RHAPSIDO must be kept out of the sight and reach of children.

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

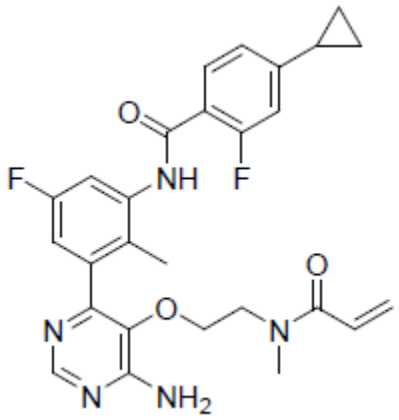
Non-proprietary name of the drug substance(s): remibrutinib

Chemical name: *N*-[3-[6-Amino-5-[2-[methyl(1-oxo-2-propen-1-yl)amino]ethoxy]-4-pyrimidinyl]-5-fluoro-2- methylphenyl]-4-cyclopropyl-2-fluorobenzamide

Molecular formula: $C_{27}H_{27}F_2N_5O_3$

Relative molecular mass: 507.54

Structural formula:



Physicochemical properties:

White to pale yellow powder.

The pH of a 1.0% (m/V) solution of remibrutinib in water/ethanol (20:80 V/V) is in the range of 7.01 - 7.58 (~25°C).

Practically insoluble in water at 25 ±0.2 °C and at 37 ±0.5 °C.

Modification A is the most thermodynamically stable form.

14. Clinical Trials

14.1. Clinical Trials by Indication

Chronic Spontaneous Urticaria

Table 4 – Summary of Patient Demographics for Clinical Trials in Chronic Spontaneous Urticaria

Study name #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean Age (range)	Sex
REMIX-1	Phase III, randomized multicenter, double-blind, placebo-controlled	Double-blind treatment period (24 weeks): RHAPSIDO 25 mg or placebo, orally, twice daily Open-label treatment period (28 weeks): RHAPSIDO 25 mg, orally, twice daily	RHAPSIDO n=313 Placebo: n=157	RHAPSIDO 44.6 years (18-79) Placebo 45.9 years (18-79)	RHAPSIDO Female 212 (67.7%) Male 101 (32.3%) Placebo Female 109 (69.4%) Male 48 (30.6%)
REMIX-2	Phase III, randomized multicenter, double-blind, placebo-controlled	Double-blind treatment period (24 weeks): RHAPSIDO 25 mg or placebo, orally, twice daily Open-label treatment period (28 weeks): RHAPSIDO 25 mg, orally, twice daily	RHAPSIDO n=297 Placebo: n=153	RHAPSIDO 41.9 years (18-80) Placebo 41.3 years (18-81)	RHAPSIDO Female 197 (65.7%) Male 103 (34.3%) Placebo Female 100 (64.5%) Male 55 (35.5%)

The efficacy and safety of RHAPSIDO were evaluated in two identical, multicenter, randomized, double-blind, placebo-controlled Phase III studies (REMIX-1 and REMIX-2) in adult patients with CSU who remained symptomatic despite treatment with second generation H1 antihistamines. Patients who completed the open-label treatment period on treatment (Week 52) had an option to enter an extension study.

REMIX-1 and REMIX-2, patients were randomized in a 2:1 ratio to receive either RHAPSIDO 25 mg or placebo, respectively, twice daily via the oral route for 24 weeks during the double-blind treatment period.

REMIX-1 and REMIX-2 enrolled a total of 925 adult patients, diagnosed with CSU, that was inadequately controlled despite treatment with second generation 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 to 42), a weekly itch severity score (ISS7) ≥6 (range 0 to 21) and a weekly hives severity score (HSS7) ≥6 (range 0 to 21) for 7 days prior to randomization.

During the placebo-controlled period, the cumulative exposure was 261.57 patient-years for the remibrutinib 25 mg b.i.d. group and 129.55 patient-years for the placebo group.

Over the entire study period, for the remibrutinib 25 mg b.i.d. group, the median duration of exposure was 52.14 weeks (range 0.1 to 60.6 weeks), with a cumulative exposure of 537.06 patient-years. For patients who transitioned to remibrutinib, the median duration of remibrutinib exposure was 28.14 weeks (range 1.1 to 32.9 weeks), with a cumulative remibrutinib exposure of 134.48 patient-years.

Demographics and baseline characteristics were generally well balanced across all groups. In REMIX-1 and REMIX-2, the median age was 45 years (range: 18-79 years) and 41 years (range: 18-81 years), with 9.6% and 7.7% ≥65 years of age and 68.3% and 65.3% female patients, respectively. Patients had a mean UAS7 of 30.28 and 29.99, a mean ISS7 of 14.59 and 14.15, and a mean HSS7 of 15.69 and 15.84, respectively. At baseline, 63.4% and 59.1% of the patients had severe disease (UAS7 ≥28) and 35.1% and 38.7% had moderate disease (UAS7 16 and <28), respectively. 51.7% and 46.6% of patients had previous experience of angioedema in REMIX-1 and REMIX-2, respectively. 68.1% and 69.2% of patients were anti-IgE biologic naive in REMIX-1 and REMIX-2, respectively. The most common prior anti-IgE biologic used was omalizumab (19.5% and 19.0% in REMIX-1 and REMIX-2, respectively).

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 39.4% and 29.5% of patients having had a duration of CSU >5 years.

The primary endpoint for the pivotal studies was:

- absolute change from baseline in UAS7 at Week 12.

The secondary endpoints for the pivotal studies were:

- absolute change from baseline in ISS7 and HSS7 at Week 12
- proportion of patients who achieved well-controlled disease (UAS7 ≤6) at Weeks 2 and 12
- proportion of patients who achieved complete absence of itch and hives (UAS7=0) at Week 12
- proportion of patients who achieved Dermatology Life Quality Index (DLQI) score = 0-1 (yes/no) at Week 12
- number of weeks with sustained disease activity control (UAS7 ≤6) up to Week 12
- number of angioedema-free weeks (weekly angioedema activity score [AAS7] = 0) up to Week 12.

Clinical response

In both REMIX-1 and REMIX-2, the primary and all secondary endpoints were met and showed statistically significant improvement in itch and hives symptoms in patients treated with remibrutinib compared to patients given placebo. Results are presented in Table 5.

Table 5 – Efficacy results in REMIX-1 and REMIX-2 at Week 12[a,b]

	REMIX-1		REMIX-2	
	RHAPSIDO (N=309)[c]	**Placebo (N=153)[c]**	**RHAPSIDO (N=297)[c]**	**Placebo (N=153)[c]**
Change from baseline in UAS7 at Week 12				
LS mean (SE) CFB	-20.02 (0.716)	-13.79 (0.980)	-19.41 (0.702)	-11.73 (0.948)
Difference in LS mean (SE) vs placebo	-6.22 (1.136)		-7.68 (1.136)	
95% CI for difference	-8.45, -4.00		-9.91, -5.46	
Change from baseline in ISS7 at Week 12				
LS mean (SE) CFB	-9.52 (0.343)	-6.89 (0.470)	-8.95 (0.335)	-5.72 (0.454)
Difference in LS mean (SE) vs placebo	-2.63 (0.544)		-3.23 (0.545)	
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 (0.401)	-6.86 (0.548)	-10.47 (0.394)	-6.00 (0.531)
Difference in LS mean (SE) vs placebo	-3.61 (0.635)		-4.47 (0.634)	
95% CI for difference	-4.85, -2.36		-5.71, -3.23	
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	
Proportion of patients with DLQI = 0-1 response at Week 12				
n (%)	120 (39.0)	34 (22.2)	106 (35.7)	28 (18.3)
Treatment difference	17.65		18.21	
(95% CI)	9.14, 26.16		9.96, 26.45	
Cumulative number of weeks with AAS7 = 0 between baseline and Week 12				
LS mean (SE)	8.43 (0.274)	6.72 (0.330)	8.81 (0.308)	6.68 (0.343)

	REMIX-1		REMIX-2	
	RHAPSIDO (N=309)[c]	**Placebo (N=153)[c]**	**RHAPSIDO (N=297)[c]**	**Placebo (N=153)[c]**
Rate ratio	1.25		1.32	
(95% CI)	(1.12, 1.41)		(1.17, 1.49)	
Cumulative number of weeks with UAS7 ≤6 between baseline and Week 12				
LS mean (SE)	5.17 (0.414)	1.92 (0.241)	4.50 (0.464)	1.38 (0.216)
Rate ratio	2.69		3.26	
(95% CI)	(2.01, 3.61)		(2.26, 4.71)	

LS mean: Least squares mean, SE: standard error, CFB: change from baseline, CI: confidence interval, UAS7: weekly urticaria activity score, ISS7 score: weekly itch severity score, HSS7: weekly hive severity score, DLQI: dermatology life quality index, AAS7: weekly angioedema activity score.
[a]All endpoints with nominal one-sided p<0.001
[b]One endpoint from Week 2 (all other endpoints are from Week 12)
[c]Multiple imputation techniques were implemented for missing data

Data from Table 5 demonstrates the superior efficacy of RHAPSIDO over placebo across all primary and secondary endpoints in adult patients with CSU who remain symptomatic despite H1-AH treatment. RHAPSIDO showed greater reduction from baseline in UAS7, ISS7, and HSS7 scores at Week 12.

These results indicated that RHAPSIDO provided statistically significant and clinically meaningful improvement in signs and symptoms of CSU (itch and hives) and patients' dermatology-related QoL.

Exploratory data in Figures 1 and 2 indicate an improvement in mean change from baseline in UAS7, observed as early as week 1 in the 24-week double-blind treatment period.

Figure 1 Mean change from baseline in UAS7 up to Week 24 in REMIX-1 (observed data)

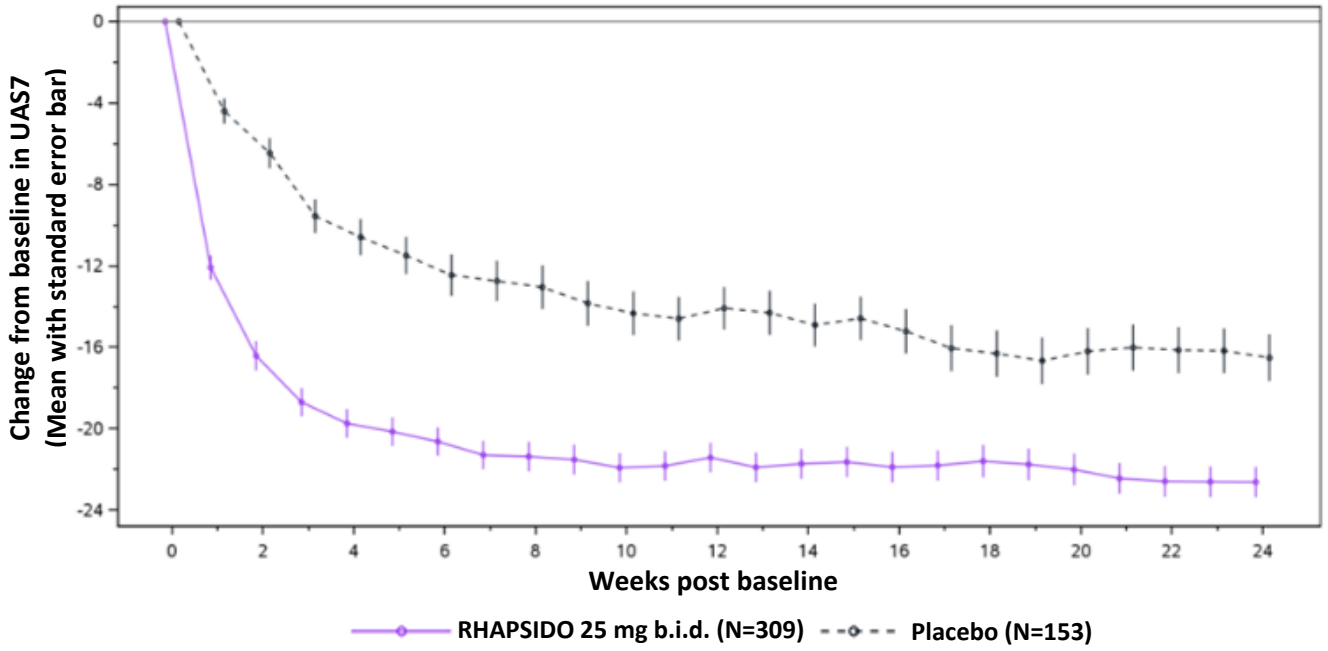
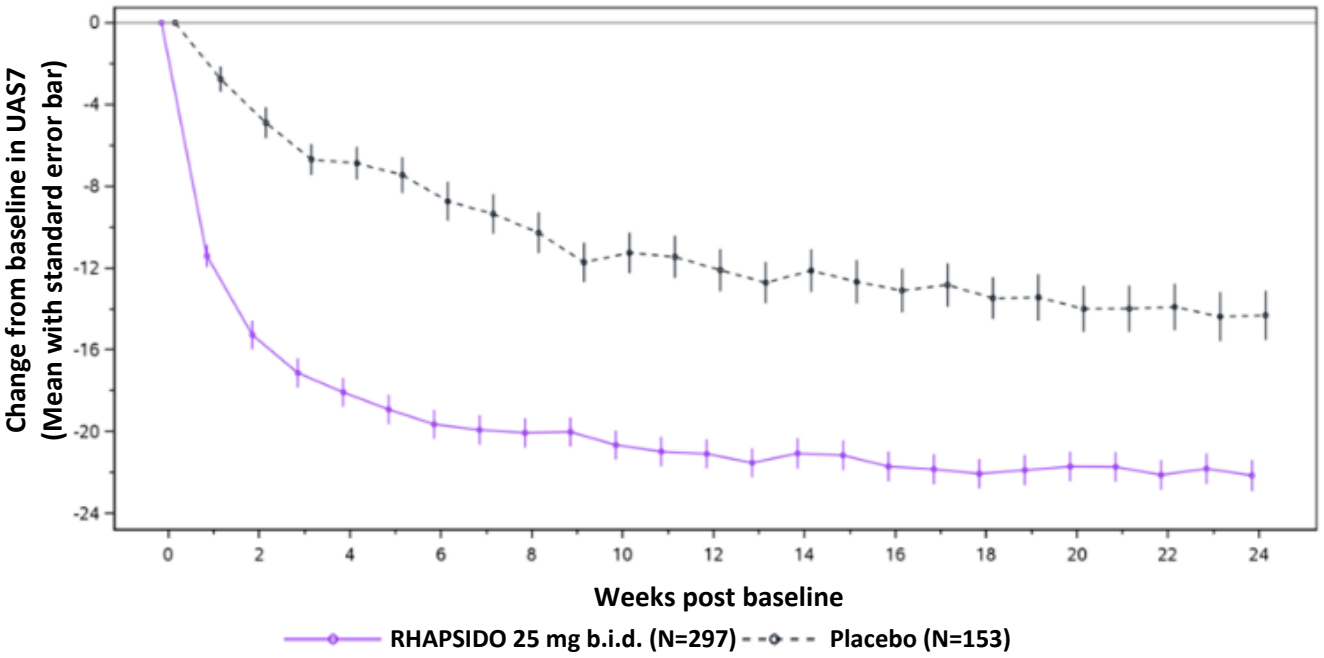


Figure 2 Mean change from baseline in UAS7 up to Week 24 in REMIX-2 (observed data)



An exploratory analysis demonstrated a consistent treatment benefit with RHAPSIDO over placebo across subgroups including prior exposure to anti-IgE biologics and total IgE level.

During the 24-week placebo-controlled period of the pooled REMIX-1 and REMIX-2 clinical studies, the overall incidence of adverse events was comparable between the remibrutinib 25 mg b.i.d. and placebo groups. Treatment discontinuations due to adverse events were infrequent and comparable, with 2.8% vs. 2.9% of patients in the remibrutinib 25 mg b.i.d. and placebo groups discontinuing treatment due to adverse events, respectively.

16. Non-Clinical Toxicology

General toxicology:

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, carcinogenic potential, and phototoxicity. However, the non-clinical safety data demonstrated effects on immune cells (inhibition of primary antibody responses) and hemostasis (inhibition of specific platelet functions).

Safety pharmacology and repeat dose toxicity

No effects on respiratory or CNS function were identified in a safety pharmacology study in rats up to the highest tested dose of 1000 mg/kg. Assessment of cardiovascular safety pharmacology showed inhibition of hERG in vitro with an IC50 of 1.4 µM (exposure multiple of 222-fold compared to unbound plasma C_{max} at the MRHD of 25 mg twice daily). Furthermore, remibrutinib induced small increases in QTc interval at high exposure (C_{max}-based exposure multiple of 28-fold [total blood] or 53-fold [unbound plasma] compared to the MRHD of 25 mg twice daily) in a non-GLP cardiovascular assessment study in dogs but not in any pivotal dog study.

In the 26-week rat study, adverse pancreas effects were observed across dose levels, and considered to represent a rat-specific change unlikely to translate to humans. In the 39-week dog study, a NOAEL was established at the highest tested dose of 300 mg/kg/day. Exposure multiples in rats and dogs ranged from approximately 15- to 146-fold ($AUC_{0\text{-}24h}$) or 8- to 100-fold (C_{max}) relative to the MRHD of 25 mg twice daily. The multiples are defined by maximal achievable exposures.

Remibrutinib inhibited primary antibody responses in rodent pharmacology studies and increased rat tail bleeding time in hemostasis assessments. These observations were considered related to effects of remibrutinib on specific B cell and platelet functions, respectively.

Genotoxicity: Remibrutinib did not show any genotoxic potential in a standard battery of assays.

Carcinogenicity: Remibrutinib did not show evidence of carcinogenic potential in mouse and rat carcinogenicity studies.

Reproductive and developmental toxicology:

In embryo-fetal development (EFD) studies in pregnant animals, remibrutinib was administered orally to rats at doses up to 1000 mg/kg/day and to rabbits at doses of 100, 300 and 450 mg/kg/day during the period of organogenesis. In rats and rabbits, both maternal and embryo-fetal NOAEL were established at 1000 mg/kg/day and 100 mg/kg/day respectively, which is equivalent to 126 and

23 times the MRHD of 25 mg twice daily based on AUC. 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 in rabbits 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 the pre- and postnatal development (PPND) study, remibrutinib was administered orally to maternal rats at doses up to 1000 mg/kg/day from gestation day 6 to lactation day (LD) 21. Remibrutinib induced adverse effects at 1000 mg/kg/day, 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. NOAEL for maternal animals and offspring was established at 300 mg/kg/day which is equivalent to 67 times the MRHD of 25 mg twice daily based on AUC.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]RHAPSIDO®

remibrutinib tablets

This Patient Medication Information is written for the person who will be taking **RHAPSIDO**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **RHAPSIDO**, talk to a healthcare professional.

What RHAPSIDO is used for:

RHAPSIDO is a prescription medicine used to treat a skin condition called chronic spontaneous urticaria. It is used in adults who continue to have symptoms despite treatment with antihistamines.

Chronic spontaneous urticaria is an unpredictable skin disease that is believed to be autoimmune in nature. Chronic spontaneous urticaria symptoms last at least 6 weeks and include the spontaneous and recurrent appearance of itchy wheals (hives), angioedema (swelling under the skin), or both.

How RHAPSIDO works:

RHAPSIDO works by blocking an enzyme in the body called Bruton's tyrosine kinase (BTK). When BTK is blocked, the release of histamine and other substances that cause inflammation is reduced. This helps to reduce the symptoms of chronic spontaneous urticaria.

The ingredients in RHAPSIDO are:

Medicinal ingredient(s): remibrutinib

Non-medicinal ingredients:

Tablet core: copovidone, croscarmellose sodium, mannitol, microcrystalline cellulose, sodium lauryl sulfate, sodium stearyl fumarate.

Tablet coating: polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172).

RHAPSIDO comes in the following dosage form(s):

Tablets; 25 mg.

The tablets are light yellow and round, curved, unscored with "LV" debossed on one side and the "Novartis" logo on the other side. The tablet diameter is 7 mm.

Do not use RHAPSIDO if:

- You are allergic to remibrutinib, or to any of the ingredients in RHAPSIDO.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RHAPSIDO. Talk about any health conditions or problems you may have, including if you:

- Have had a recent surgery or plan to have surgery. Your healthcare professional may tell you to stop taking RHAPSIDO for 3 to 7 days before and after any planned medical or surgical procedures.
- Have bleeding problems or are taking a blood thinner medication.
- Have liver problems.
- Have recently received or are scheduled to receive an immunization (vaccine).
- Are pregnant, think you may be pregnant or are planning to become pregnant.
- Are breastfeeding, or plan to breastfeed.

Other warnings you should know about:

Pregnancy: RHAPSIDO may harm your unborn baby. If you become pregnant during treatment with RHAPSIDO, talk to a healthcare professional **right away**. If you are a woman who could become pregnant, you must use effective contraception during your treatment and for at least 1 week after stopping RHAPSIDO treatment.

Risk of bleeding: Bleeding may occur during your treatment with RHAPSIDO. Your healthcare professional will monitor you for signs and symptoms of bleeding and may stop your treatment if bleeding happens. Tell your healthcare professional 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

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with RHAPSIDO:

- Medicines used to treat HIV infection, such as ritonavir.
- Medicines used to treat certain types of seizures (epilepsy), such as carbamazepine.
- Medicines used to treat heart problems such as digoxin.
- Medicines used to treat high cholesterol such as rosuvastatin.
- Medicines used to relieve pain, reduce fever or prevent blood clots such as aspirin (acetylsalicylic acid).
- Medicines used to treat blood clots such as clopidogrel.
- Medicines used to thin the blood such as warfarin.

How to take RHAPSIDO:

- Always take RHAPSIDO exactly as your healthcare professional has told you to. Check with your healthcare professional if you are not sure.

- Take RHAPSIDO tablets by mouth. Swallow the tablet whole with water. Do not split, crush, chew or break the tablet before swallowing.
- RHAPSIDO can be taken with or without food.
- Taking RHAPSIDO at the same time each day will help you to remember when to take your medicine.

Usual dose:
The usual recommended dose is 25 mg (one tablet) twice daily.

Overdose:

If you think you, or a person you are caring for, have taken too much RHAPSIDO, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you miss a dose or doses, skip the missed dose and take your next dose at the regularly scheduled time. Do not take a double dose to make up for a forgotten dose.

Possible side effects from using RHAPSIDO:

These are not all the possible side effects you may have when taking RHAPSIDO. If you experience any side effects not listed here, tell your healthcare professional.

- Cold-like symptoms (upper respiratory tract infection)
- Bleeding (including purple or red spots on or under the skin, bruising, bleeding gums, nosebleed, bright red spot (broken blood vessel) in the white of the eye)
- Headache
- Nausea
- Stomach pain

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Do not store above 30°C.
- Keep out of reach and sight of children.
- Do not take this medicine after the expiration date listed on the carton.
- Ask your pharmacist how to dispose of medicines you no longer use.

If you want more information about RHAPSIDO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.novartis.ca); or by calling 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

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RHAPSIDO is a registered trademark.