▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – RHAPSIDO (REMIBRUTINIB) TABLETS

1 NAME OF THE MEDICINE

Remibrutinib.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 25 mg of remibrutinib.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Light yellow, round, curved, unscored film-coated tablet with diameter 7 mm, debossed with "LV" on one side and "Novartis" logo ( ) on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Chronic spontaneous urticaria (CSU)

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage regimen

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

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.

Dose interruption

Consideration should be given to withholding 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 4.8 Adverse effects (Undesirable effects) and 4.5 Interactions with other medicines and other forms of interaction).

Method of 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 (see section 5.1 Pharmacodynamic properties).

Special populations

Renal impairment

No dose adjustment of RHAPSIDO is required in patients with renal impairment. Elimination of unchanged remibrutinib via the kidney is negligible (<1%). There are limited data available in patients with severe renal impairment (see section 5.1 Pharmacodynamic properties).

Hepatic impairment

No dose adjustment of RHAPSIDO is required in patients with mild or moderate, or hepatic impairment. RHAPSIDO is not recommended in patients with severe hepatic impairment (see section 5.1 Pharmacodynamic properties).

Paediatric patients (below 18 years)

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

Elderly patients *(*65 years of age or above)

No relevant pharmacokinetic differences have been observed in elderly (≥65 years) patients compared to the overall population. Therefore, no dose adjustment is required in patients 65 years of age or above (see section 5.1 Pharmacodynamic properties).

4.3 CONTRAINDICATIONS

None.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Risk of Bleeding

Mild to moderate mucocutaneous bleeding events have occurred in patients treated with remibrutinib. The most frequently reported events were bruising-related, such as petechiae and contusion (see section 4.8 Adverse effects (Undesirable effects)).

Patients receiving antithrombotic agents with remibrutinib may be at an increased risk of bleeding. The risks and benefits of co-administration of antithrombotic agents with remibrutinib must be considered (see section 4.5 Interactions with other medicines and other forms of interactions).

Patients should be instructed to seek medical advice if signs and symptoms suggestive of significant bleeding occur. If significant bleeding is suspected, treatment with remibrutinib should be interrupted. Upon resolution, treatment may be resumed if the benefit is expected to outweigh the risk.

Withholding remibrutinib treatment should be considered for 3 to 7 days before surgery and for 3 to 7 days after surgery depending upon the type of surgery and risk of bleeding (see section 4.2 Dose and method of administration).

Live Attenuated Vaccines

The safety of RHAPSIDO with live or live-attenuated vaccines has not been studied. Vaccination with live or live-attenuated vaccines is therefore not recommended during treatment with RHAPSIDO (see section 4.5 Interactions with other medicines and other forms of interactions).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of other drugs on RHAPSIDO

In vitro, remibrutinib is metabolised predominantly via CYP3A4 and is a substrate for the P-glycoprotein transporter protein.

CYP3A4 inhibitors

Avoid use of 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 remibrutinib 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

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

Effect of remibrutinib on other drugs

In vitro, remibrutinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and systemic CYP3A4/5 at clinically relevant concentrations. Remibrutinib is a time-dependent inhibitor of intestinal CYP3A4/5 and an inducer of CYP1A2, CYP2B6, CYP2C9 and CYP3A4/5.

Remibrutinib is not an inhibitor of BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, MATE2-K or MRP2 or NTCP at clinically relevant concentrations *in vitro*. Accordingly, no notable interactions with other drug products caused by Remibrutinib through such mechanisms are anticipated in patients. Remibrutinib inhibits P-glycoprotein and BCRP *in vitro*.

P-gp or BCRP substrates

Caution is required when using remibrutinib 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 remibrutinib 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 remibrutinib 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).

Immune response to vaccines

No data are available on the effects of live or live-attenuated vaccines in patients receiving remibrutinib and these vaccines should not be co-administered with remibrutinib.

Non-live vaccines can be given during remibrutinib treatment. To optimize the immune response with non-live vaccines, benefit-risk of treatment interruption of remibrutinib (1 week prior to a planned vaccination until 2 weeks after the vaccination) may be considered (see section 5.2 Pharmacokinetic properties).

Antithrombotic agents

No data are available on co- administration of remibrutinib with anticoagulants. Co-administration of remibrutinib 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 remibrutinib clinical studies. The risks and benefits of co-administration of antithrombotic agents with remibrutinib must be considered (see sections 4.2 Dose and method of administration and 4.8 Adverse effects (Undesirable effects)).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effect of remibrutinib 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 19 times for males the MRHD of 25 mg twice daily based on AUC.

Use in pregnancy – Pregnancy Category D

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

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 doses of 300mg/kg/day (121 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) of 100 mg/kg/day (20 times the MRHD based on AUC). 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 108 times the MRHD based on AUC.

Contraception

Females

Sexually active females of reproductive potential should consider using 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.

Use in lactation

It is unknown whether remibrutinib 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 remibrutinib and for 1 week after the last dose.

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 58 times the MRHD of 25 mg twice daily based on AUC.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

Summary of the safety profile

The safety profile of RHAPSIDO is based on the pooled data set (N=912) of two Phase III studies, REMIX-1 (NCT05030311) and REMIX-2 (NCT05032157) 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%). Severity of all the ADRs was mild to moderate. No severe ADRs were reported.

Tabulated summary of adverse drug reactions from clinical trials

ADRs from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each ADR is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1 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 N=606 n (%) 25 mg twice daily**	**Placebo N=306 n (%)**	**Frequency category**
Infections and infestations			
Upper respiratory tract infections[1)]	89 (14.7%)	36 (11.8%)	Very common
Skin and subcutaneous tissue disorders			
Petechiae	23 (3.8%)	1 (0.3%)	Common
Contusion[2)]	14 (2.3%)	2 (0.7%)	Common
Ecchymosis	9 (1.5%)	1 (0.3%)	Common
Purpura	5 (0.8%)	0 (0.0%)	Uncommon
Vascular disorders			
Epistaxis	5 (0.8%)	1 (0.3%)	Uncommon
Conjunctival bleeding	2 (0.3%)	0 (0.0%)	Uncommon
Gingival bleeding	1 (0.2%)	0 (0.0%)	Uncommon

[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 contusion, increased tendency to bruise, haematoma

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 (listed in Table 7-1 under "Skin and subcutaneous tissue disorders and Vascular disorders") occurred in 7.8% of patients treated with RHAPSIDO (exposure adjusted incidence rate [EAIR] 18.8 per 100 patient - years) compared to 1.6% (EAIR 3.8 per 100 patient - years) in the placebo group. In patients treated with RHAPSIDO, 92.0% of these events were mild and 8.0% were moderate in severity, compared to 80.0% and 20.0% 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% (6/606) experienced events that led to RHAPSIDO interruption, while none of these events occurred in the placebo group (see sections 4.2 Dose and method of administration and 4.5 Interactions with other medicines and other interactions).

During the entire study period of up to 52 weeks, mucocutaneous bleeding events occurred in 8.3% of patients treated with RHAPSIDO (EAIR 9.7 per 100 patient - years). 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.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Bruton's tyrosine kinase inhibitors.
Anatomical Therapeutic Chemical (ATC) code: L04AA60.

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 signalling via Fc epsilon receptor-1 (FcεRI), Fc gamma receptors (FcγR) and the B cell antigen receptor (BCR).

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

Pharmacodynamic effects

Inhibition of mast cells and basophils by remibrutinib results in reduced secretion of mast cell mediators such as histamine, as well as reduction of blood basophil surface markers for degranulation such as CD63 and CD203c. In addition, remibrutinib inhibits activation of autoreactive B cells via BCR and reduces antigen presentation markers such as CD69 and CD86.

Clinical pharmacokinetic and pharmacodynamic (PK/PD) data estimated a BTK occupancy ≥96% in blood maintained over 12 hours with remibrutinib 25 mg twice daily. An exploratory translational PK/PD model showed that remibrutinib 25 mg twice daily is estimated to achieve a trough BTK occupancy ≥80% in peripheral target tissues.

Immunoglobulins

Mature B cells are not dependent on BTK for their survival and therefore remibrutinib does not lead to depletion of circulating B cells. 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 for remibrutinib and -0.59 for placebo; the mean change from baseline to minimum post-baseline value for IgM levels was -0.22 for remibrutinib and 0.08 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 electrocardiogram (ECG) variables and morphology were investigated in two Phase I studies: Study 1 included a total of 231 healthy subjects after single and multiple doses of up to 600 mg remibrutinib once daily and Study 2 included 265 patients with CSU at doses ranging from 10 mg remibrutinib once daily to 100 mg remibrutinib twice daily. Based on concentration QTc modeling data from these studies there is no clinically relevant effect (mean increase of 0.67 ms, upper bound of 90% CI 0.89 ms) of remibrutinib on the QTc interval at the clinical exposure (remibrutinib 25 mg twice daily. Based on PK modeling, an approximately 2.7-fold increase in $C_{max,ss}$ of remibrutinib (remibrutinib 25 mg twice daily) was observed when given together with a strong CYP3A4 inhibitor (high clinical exposure scenario) and was also not associated with a clinically relevant increase in QTc (mean increase of 3.18 ms, upper bound of 90% CI 4.18 ms).

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 (ABPM) at steady state (week 4) compared to baseline in a multicenter, open-label Phase III study (A2305). The Phase III study enrolled 144 patients with CSU inadequately controlled by second generation H1-antihistamine, who were administered remibrutinib 25 mg b.i.d. The upper limit of the 95% CI was -0.3 mmHg, which was less than the prespecified upper limit of an increase of 3 mmHg. No clinically relevant effect was noted at week 4 compared to baseline in 24-hour systolic blood pressure (estimated mean change -1.3 mmHg (95% CI: -2.3, -0.3)) or diastolic blood pressure (estimated mean change -0.1 (95% CI: -0.8, 0.6)). In addition, there was no clinically relevant effect on heart rate.

Clinical trials

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.

In 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 and continued in a 28-week open-label treatment period, during which all patients received RHAPSIDO 25 mg twice daily.

REMIX-1 (NCT05030311) and REMIX-2 (NCT05032157) 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.

Table 2 Baseline demographics and disease characteristics in REMIX-1 and REMIX-2

Parameters	REMIX-1			REMIX-2		
	RHAPSIDO (N=313)	Placebo (N=157)	Total (N=470)	RHAPSIDO (N=300)	Placebo (N=155)	Total (N=455)
Age (years) n (%)						
18-65 years	282 (90.1)	143 (91.1)	425 (90.4)	276 (92.0)	144 (92.9)	420 (92.3)
> 65 years	31 (9.9)	14 (8.9)	45 (9.6)	24 (8.0)	11 (7.1)	35 (7.7)
Sex n (%)						
Female n (%)	212 (67.7)	109 (69.4)	321 (68.3)	197 (65.7)	100 (64.5)	297 (65.3)
Race n (%)						
White or Caucasian	188 (60.1)	89 (56.7)	277 (58.9)	159 (53.0)	79 (51.0)	238 (52.3)
Black or African American	12 (3.8)	3 (1.9)	15 (3.2)	7 (2.3)	3 (1.9)	10 (2.2)
Asian	94 (30.0)	46 (29.3)	140 (29.8)	130 (43.3)	72 (46.5)	202 (44.4)
Ethnicity n (%)						
Hispanic/ Latino	76 (24.3)	44 (28.0)	120 (25.5)	16 (5.3)	5 (3.2)	21 (4.6)
Not Hispanic or Latino	237 (75.7)	113 (72.0)	350 (74.5)	284 (94.7)	149 (96.1)	433 (95.2)

Parameters	REMIX-1			REMIX-2		
	RHAPSIDO (N=313)	Placebo (N=157)	Total (N=470)	RHAPSIDO (N=300)	Placebo (N=155)	Total (N=455)
Disease characteristics						
Moderate activity: UAS7 16-<28 n (%)	104 (33.2)	61 (38.9)	165 (35.1)	112 (37.3)	64 (41.3)	176 (38.7)
Severe activity: UAS7 28-42 n (%)	205 (65.5)	93 (59.2)	298 (63.4)	181 (60.3)	88 (56.8)	269 (59.1)
Mean UAS7 score	30.63	29.58	30.28	30.23	29.52	29.99
Mean HSS7 score	15.89	15.29	15.69	15.93	15.67	15.84
Mean ISS7 score	14.74	14.29	14.59	14.31	13.85	14.15
Mean DLQI score	14.21	13.52	13.98	14.00	13.58	13.86
Previous experience of Angioedema n (%)	173 (55.3)	70 (44.6)	243 (51.7)	143 (47.7)	69 (44.5)	212 (46.6)
Previous exposure to anti-IgE biologics %)	98 (31.3)	52 (33.1)	150 (31.9)	90 (30.0)	50 (32.3)	140 (30.8)
Duration of CSU (years) n (%)						
Mean duration of CSU (years)	6.907	6.128	6.647	5.511	4.638	5.214
<=5 years	191 (61)	94 (59.9)	285 (60.6)	209 (69.7)	112 (72.3)	321 (70.5)
> 5 years	122 (39.0)	63 (40.1)	185 (39.4)	91 (30.3)	43 (27.7)	134 (29.5)
CU-index n (%)*						
Positive (>=10)	90 (28.8)	37 (23.6)	127 (27.0)	77 (25.7)	48 (31.0)	125 (27.5)
Negative (<10)	215 (68.7)	114 (72.6)	329 (70.0)	166 (55.3)	76 (49.0)	242 (53.2)
Total IgE level n (%)						
Normal/High (>43 IU/mL)	225 (71.9)	110 (70.1)	335 (71.3)	224 (74.7)	107 (69.0)	331 (72.7)
Low (<=43 IU/mL)	81 (25.9)	43 (27.4)	124 (26.4)	71 (23.7)	45 (29.0)	116 (25.5)

CSU: chronic spontaneous urticaria, UAS7: weekly urticaria activity score, HSS7: weekly hive severity score, ISS7 score: weekly itch severity score, DLQI: dermatology life quality index, CU-index: chronic urticaria index, IgE: Immunoglobulin E.

* Values for the missing category are not presented

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 3.

Table 3 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	
p-value	<0.001		<0.001	
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	
p-value	<0.001		<0.001	
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	
p-value	<0.001		<0.001	
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	
p-value	<0.001		<0.001	
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	
p-value	<0.001		<0.001	
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	
p-value	<0.001		<0.001	
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	

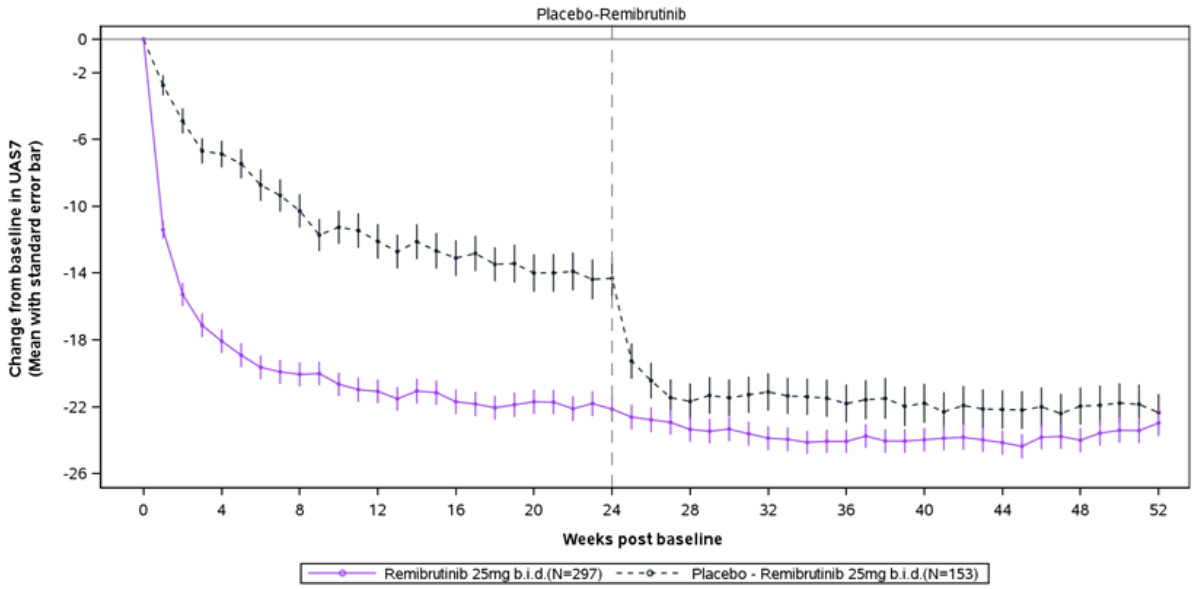
	REMIX-1		REMIX-2	
	RHAPSIDO (N=309)[c]	**Placebo (N=153)[c]**	**RHAPSIDO (N=297)[c]**	**Placebo (N=153)[c]**
(95% CI)	9.14, 26.16		9.96, 26.45	
p-value	<0.001		<0.001	
Cumulative number of weeks with AAS7 = 0 between baseline and Week 12				
LS mean (SE)	8.43 (0.274)	6.72 (0.330)	8.81 (0.308)	6.68 (0.343)
Rate ratio	1.25		1.32	
(95% CI)	(1.12, 1.41)		(1.17, 1.49)	
p-value	<0.001		<0.001	
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)	
p-value	<0.001		<0.001	

LS mean: Least squares mean, SE: standard error, CFB: change from baseline, CI: confidence interval, p-value: one-sided p-value, 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

Table 3 shows that statistically significant and clinically meaningful improvements in mean change from baseline in UAS7 score were demonstrated in REMIX-2 at Week 12 in patients treated with RHAPSIDO versus placebo.

Figure 1 shows treatment effect was observed as early as Week 1, and improvement was sustained throughout the 52 weeks. The results were similar in REMIX-1.

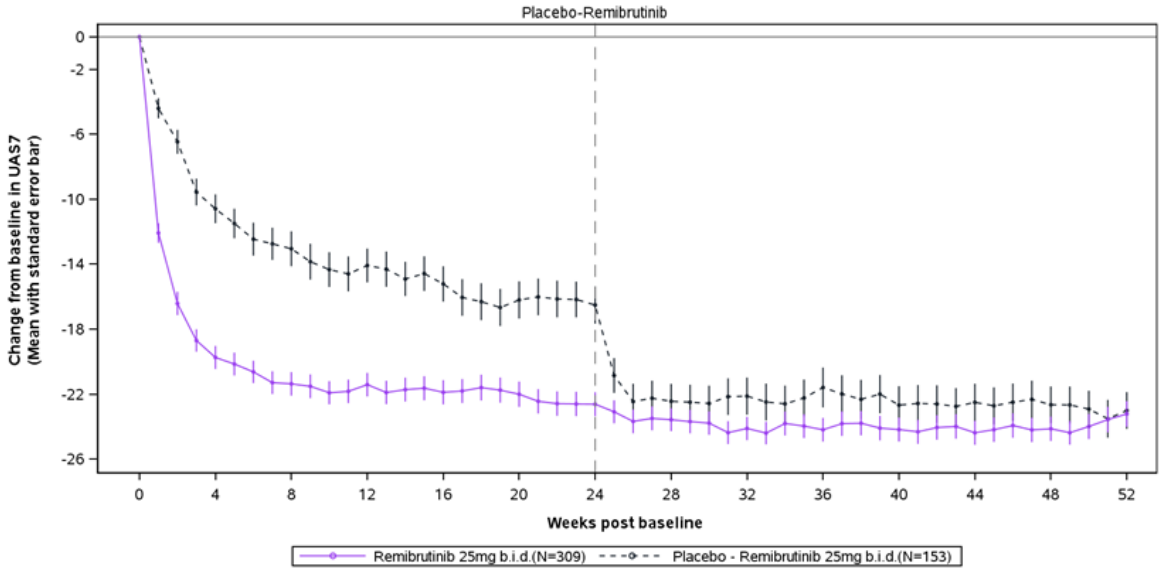
Figure 1 Mean change from baseline in weekly urticaria activity score (UAS7) over time, up to Week 52 in REMIX-2 (observed data)[a,b]



[a] In REMIX-2 at baseline, 297 patients were included in the remibrutinib arm and 153 in the placebo arm.
[b] Placebo patients switched over to receive open label remibrutinib treatment from Week 24.

Table 3 shows that statistically significant and clinically meaningful improvements in mean change from baseline in UAS7 was demonstrated in REMIX-1 at Week 12 in patients treated with RHAPSIDO vs. placebo. Figure 2 shows treatment effect was observed as early as Week 1, and improvement was sustained throughout the 52 weeks.

Figure 2 Mean change from baseline in weekly urticaria activity score (UAS7) over time, up to Week 52 in REMIX-1 (observed data)[a,b]



[a] In REMIX-1 at baseline, 309 patients were included in the remibrutinib arm and 153 in placebo arm.
[b] Placebo patients switched over to receive open label remibrutinib treatment from Week 24.

Subgroup analyses demonstrated a consistent treatment benefit with RHAPSIDO over placebo across subgroups (including duration of CSU, previous history of angioedema, CU-index, prior exposure to anti-IgE biologics and total IgE level).

5.2 PHARMACOKINETIC PROPERTIES

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

The remibrutinib AUC increased by 33% and C_{max} decreased by 5%, respectively, with a high-fat meal compared to the fasted state following administration of RHAPSIDO. RHAPSIDO may be taken with or without food.

Linearity/non-linearity

The PK of remibrutinib at steady state was approximately linear in the total daily dose range of 10 to 200 mg.

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 litres (central compartment) and 1180 litres (peripheral compartment).

Metabolism

Remibrutinib is metabolised primarily by CYP3A4, leading to the formation of 18 inactive metabolites, all in low amounts in circulation. Remibrutinib was the most abundant compound in blood (16.7%).

Excretion

Remibrutinib had a mean elimination half-life ranging between 1 and 2 hours at steady state. Following administration of 100 mg [^{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 below 1% of the dose.

Special populations

A population PK (pop-PK) analysis was 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).

Use in the elderly

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 (see section 4.2 Dose and method of administration).

Race/Ethnicity

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.

Renal impairment

Following an oral dose of 25 mg remibrutinib twice daily, the pop-PK data 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 m^2), moderate (eGFR 45 to <60 mL/min/1.73 m^2) or severe (eGFR 15 to <45 mL/min/1.73 m^2) renal impairment when compared to patients with normal renal function (see section 4.2 Dose and method of administration).

Hepatic impairment

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 (see section 4.2 Dose and method of Administration).

Vaccination immune response study

Potential effects of concomitant or interrupted (for 1 week before and 2 weeks after vaccination) use of remibrutinib in comparison to placebo on the immune response to selected non-live vaccines were investigated in a healthy volunteer study with three vaccines, an influenza vaccine (T cell-dependent), pneumococcal polysaccharide (PPV23) vaccine (T cell-independent) and keyhole limpet hemocyanin (KLH) vaccine (T cell-dependent).

Immune response was assessed based on fold-increase in antibody titers and achievement of protective antibody titer levels (influenza and PPV23 vaccine) and increase of IgG and IgM antibody levels (KLH vaccine).

The study demonstrated that, in comparison to placebo, the immune response to influenza vaccine and to PPV23 vaccine was not significantly impacted when remibrutinib was interrupted for 1 week before and 2 weeks after vaccination. Similarly, the immune response to KLH vaccine based on IgG, when compared to placebo, was not impacted by RHAPSIDO interruption, while the immune response based on IgM was lowered (23% reduction in IgM). For concomitant RHAPSIDO treatment, titer response to vaccination was generally lower in comparison to placebo. However, protective antibody titers were achieved for the majority of antigens (3 out of 4) for influenza vaccine. Concomitant RHAPSIDO treatment was associated with a 60% reduction of responders to PPV23 vaccine and lower antibody levels (21% and 25% reduction for IgG and IgM, respectively) to KLH vaccine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Remibrutinib was not mutagenic in an *in vitro* bacteria reverse mutation assay (Ames test), or clastogenic in an *in vitro* human lymphocyte chromosomal aberration assay or in an *in vivo* rat micronucleus test.

Carcinogenicity

The carcinogenic potential of remibrutinib was investigated in 2-year studies in transgenic mice and rats following oral administration of remibrutinib. Remibrutinib was not carcinogenic in either species up to the highest dose levels tested: 1500 mg/kg/day in mice (50 and 124-times the clinical exposure at the maximum recommended human dose (MRHD) in male and female mice, respectively) and 300 mg/kg/day in rats (7 and 84-times the clinical exposure at the MRHD in male and female rats, respectively).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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

Tablet coating: polyvinyl alcohol, titanium dioxide, iron oxide yellow, iron oxide red, purified talc, macrogol 4000.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Store in original container.

6.5 NATURE AND CONTENTS OF CONTAINER

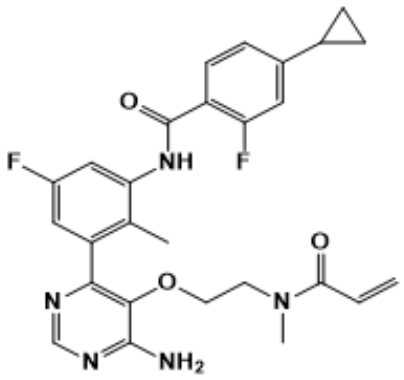
RHAPSIDO is supplied as 25 mg film-coated tablets in PA/Al/PVC/Al blisters in either packs of 30 tablets or 60 tablets in a cardboard carton, or multipacks containing 180 tablets (3 packs of 60).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

1787294-07-8.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – PRESCRIPTION ONLY MEDICINE.

8 SPONSOR

Novartis Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
54 Waterloo Road
Macquarie Park NSW 2113

Ph: 1800 671 203

Website: www.novartis.com.au
®= Registered Trademark

9 DATE OF FIRST APPROVAL

11 May 2026

10 DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information

Internal document code: rha110526i based on CDS dated 3 February 2025