ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Rhapsido 25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 25 mg remibrutinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Light yellow, round, curved film-coated tablet with a diameter of 6.7 to 7.6 mm, debossed with “LV” on one side and with the company logo on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rhapsido is indicated for the treatment of chronic spontaneous urticaria (CSU) in adult patients with inadequate response to H1 antihistamine treatment.

4.2 Posology and method of administration

Treatment should be initiated by physicians experienced in the diagnosis and treatment of chronic spontaneous urticaria.

Posology

The recommended dose of remibrutinib is 25 mg taken orally twice daily, once in the morning and once in the evening.

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

Prescribers are advised to periodically reassess the need for continued therapy. Consideration should be given to discontinuing treatment in patients who have shown no response after 24 weeks of treatment for CSU.

Dose interruption
It is recommended to interrupt remibrutinib 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 4.4, 4.5 and 4.8).

Special populations
Elderly
No specific dose adjustment is required for elderly patients (aged ≥65 years) (see section 5.2). Limited data are available on the use of remibrutinib in patients older than 65 years.

Renal impairment
No dose adjustment is required in patients with renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment. Remibrutinib is not recommended for use in patients with severe hepatic impairment (see section 5.2).

Paediatric population
Rhapsido should not be used in infants and children below 6 years of age because of the unknown potential impact on humoral immunity maturation (e.g. generation of protective immunoglobulins and memory B cells).

The safety and efficacy of remibrutinib in children and adolescents 6 to 18 years of age have not been established. No data are available.

Method of administration

Oral use.

Remibrutinib may be taken with or without food. Patients should be instructed to swallow the tablet whole with water. The tablets should not be split, crushed or chewed to ensure the entire dose is delivered correctly.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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).

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).

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.

Interruption of remibrutinib treatment is recommended 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).

Vaccinations

The safety of remibrutinib with live or live-attenuated vaccines has not been studied. Vaccination with live or live-attenuated vaccines is therefore not recommended during treatment with remibrutinib (see section 4.5).

The safety of remibrutinib with non-live vaccines has been studied, therefore non-live vaccines can be given during remibrutinib treatment. To optimise the immune response to non-live vaccines, interruption of remibrutinib treatment should be considered (from 1 week prior to the planned vaccination until 2 weeks after the vaccination) (see section 4.5).

Interactions

Remibrutinib is a substrate of cytochrome P450 enzyme 3A4 (CYP3A4), therefore there is a potential for interaction with other concomitantly administered medicinal products that are metabolised by or modulate the activity of CYP3A4 (see section 4.5).

Concomitant use with strong CYP3A4 inhibitors increases remibrutinib exposure and consequently may increase the risk for adverse reactions with remibrutinib. Concomitant use with strong CYP3A4 inhibitors must be avoided (see section 4.5).

Concomitant use with moderate or strong CYP3A4 inducers decreases remibrutinib exposure and consequently may decrease the efficacy of remibrutinib. Concomitant use with moderate or strong CYP3A4 inducers must be avoided (see section 4.5).

It is recommended to monitor patients more frequently for potential adverse reactions when remibrutinib is used with P-glycoprotein (P-gp) substrates and breast-cancer resistance protein (BCRP) substrates with a narrow therapeutic index (see section 4.5).

Excipient with known effect

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Remibrutinib is primarily metabolised by CYP3A4.

Active substances that may increase remibrutinib blood concentrations

CYP3A4 inhibitors
Co-administration of remibrutinib with strong CYP3A4 inhibitors must be avoided. Co-administration of ritonavir, a strong CYP3A4/P-gp inhibitor, led to a 4.3-fold increase in the AUC and a 3.3-fold increase in the C_{max} of remibrutinib.

Active substances that may decrease remibrutinib blood concentrations

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 78% (AUC).

Active substances whose plasma concentrations may be altered by remibrutinib

Transport substrates/inhibitors
It is recommended to monitor patients more frequently for potential adverse reactions when using remibrutinib with P-gp and BCRP substrates with a narrow therapeutic index, especially where minimal concentration changes can lead to adverse reactions. Co-administration of digoxin (a P-gp substrate with a narrow therapeutic index) with remibrutinib led to a 1.4-fold increase in the AUC and a 2.1-fold increase in the C_{max} of digoxin. Co-administration of rosuvastatin (a BCRP substrate without a narrow therapeutic index) with remibrutinib led to a 1.7-fold increase in the AUC and a 1.6-fold increase in the C_{max} of rosuvastatin.

In a drug-interaction study, the effect of administration of remibrutinib (100 mg twice daily) on the pharmacokinetics of midazolam (a sensitive CYP3A4 substrate) led to a 43% increase in the AUC and a 27% increase in the C_{max} of midazolam. The effect of the clinical dose of remibrutinib (25 mg twice daily) was not studied and may be different. Remibrutinib should not be used with concomitant administration of CYP3A4 substrates that have narrow therapeutic indices (e.g. ciclosporin, tacrolimus, digoxin, warfarin, carbamazepine).

Oral contraceptives
Co-administration of remibrutinib is not expected to have an adverse impact on the efficacy of oral contraceptives containing ethinyloestradiol and levonorgestrel (CYP3A4 substrates) as their exposure was not decreased in the presence of remibrutinib 100 mg twice daily (1.28- and 1.36-fold increase in C_{max} and 1.16- and 1.39-fold increase in AUC, respectively).

Effect of remibrutinib on 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 (see section 4.4).

Based on a vaccination immune response study in healthy volunteers, non-live vaccines can be given during remibrutinib treatment. To optimise the immune response to non-live vaccines, interruption of remibrutinib treatment should be considered (from 1 week prior to the planned vaccination until 2 weeks after the vaccination).

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, concomitant remibrutinib treatment was associated with a 60% reduction of responders to the T cell-independent polysaccharide PPV23 vaccine, a 21% reduction in IgG response to keyhole limpet haemocyanin (KLH) vaccine (T cell-dependent neoantigen), comparable response rates (1 to 14% reduction) for 3 out of 4 of the antigens in influenza vaccine (T cell-dependent) and a 27% reduction for 1 out of 4 of the influenza antigens.

Effect of remibrutinib on antithrombotic agents

No data are available on co-administration of remibrutinib with anticoagulants. The risks and benefits of co-administration of antithrombotic agents with remibrutinib must be considered (see sections 4.2, 4.4 and 4.8).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Sexually active women of childbearing potential must use effective contraception (methods that result in less than 1% pregnancy rates) during remibrutinib treatment and for at least 1 week after the last dose. Women of childbearing potential must be advised that animal studies have shown remibrutinib to be harmful to the developing foetus (see section 5.3).

Pregnancy

There are limited data from the use of remibrutinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Rhapsido is not recommended during pregnancy.

Breast-feeding

It is unknown whether remibrutinib/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with remibrutinib and for 1 week after the last dose.

Fertility

There are no data on the effect of remibrutinib on human fertility. No adverse effects on fertility were observed in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Rhapsido has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reaction is upper respiratory tract infections (14.7%) such as nasopharyngitis (6.6%) and influenza (2.5%).

Tabulated list of adverse reactions

Adverse reactions are listed according to MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse reaction is defined as: 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); not known (cannot be estimated from available data).

Table 1 Adverse reactions*

System organ class	Adverse reaction	Frequency
Infections and infestations	Upper respiratory tract infections[1]	Very common
	Herpes virus infections[2]	Common
Nervous system disorders	Headache	Common
Vascular disorders	Bruising	Common
	Petechiae	Common
	Contusion[3]	Common
	Ecchymosis	Common
	Purpura	Uncommon
	Bleeding	Common
	Haematuria	Common
	Epistaxis	Uncommon
	Conjunctival bleeding	Uncommon
	Gingival bleeding	Uncommon
Gastrointestinal disorders	Nausea	Common
	Abdominal pain	Common
Musculoskeletal and connective tissue disorders	Back pain	Common
General disorders and administration site conditions	Pyrexia	Common

* 24-week placebo-controlled phase III studies in CSU

[1] Upper respiratory tract infections include preferred terms: 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] Herpes virus infections include preferred terms: herpes simplex, herpes zoster, oral herpes

[3] Contusion includes preferred terms: contusion, increased tendency to bruise, haematoma

The safety profile of remibrutinib in patients treated for up to 52 weeks in REMIX-1 and REMIX-2 remained consistent with the adverse reactions reported in Table 1.

Description of selected adverse reactions

Mucocutaneous bleeding events

In the 24-week placebo-controlled, double-blind treatment period of the pooled dataset (REMIX-1 and REMIX-2 phase III studies), mucocutaneous bleeding events (listed in Table 1 under "Vascular disorders") occurred in 7.8% of patients treated with remibrutinib. The most frequently reported events were bruising-related: petechiae (3.8%) and contusion (2.3%). Overall, in patients treated with remibrutinib, 92.0% of these events were mild and 8.0% were moderate in severity. The median time to onset was 25 days and the median duration was 22 days. All cases resolved spontaneously without additional treatment. No association between mucocutaneous bleeding events and low platelet counts was observed. Co-administration of remibrutinib with anticoagulants was not allowed in clinical studies, but co-administration with antiplatelet agents (acetylsalicylic acid (≤100 mg/day) or clopidogrel (≤75 mg/day)) was permitted (see sections 4.4 and 4.5).

In patients treated with remibrutinib, 0.5% experienced mucocutaneous bleeding events that led to remibrutinib discontinuation and 1.0% led to remibrutinib interruption (see sections 4.2, 4.4 and 4.5).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

There was no evidence of dose-limiting adverse events seen with remibrutinib at doses up to 600 mg per day in the phase I clinical studies. Signs and symptoms of remibrutinib overdose have not been established and there is no specific treatment for remibrutinib overdose.

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: Immunosuppressants, selective immunosuppressants, ATC code: L04AA60

Mechanism of action

Remibrutinib is a selective Bruton's tyrosine kinase (BTK) inhibitor that forms a covalent bond with a cysteine residue in the BTK active site, leading to durable inactivation of BTK. The therapeutic effect of remibrutinib in CSU is achieved through inhibition of 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.

Pharmacodynamic effects

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.

Clinical efficacy and safety

The efficacy and safety of remibrutinib were evaluated in two identical, multicentre, randomised, double-blind, placebo-controlled phase III studies (REMIX-1 and REMIX-2) in adult patients with inadequately controlled CSU despite treatment with second-generation H1 antihistamines.

In REMIX-1 and REMIX-2, patients were randomised in a 2:1 ratio to receive either remibrutinib 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 remibrutinib 25 mg twice daily.

REMIX-1 and REMIX-2 enrolled a total of 925 adult patients diagnosed with CSU that was inadequately controlled despite treatment with a standard dose of a second-generation H1 antihistamine 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 randomisation. In addition to all patients receiving a stable dose of a second-generation H1 antihistamine (background therapy), patients were allowed to use another second-generation H1 antihistamine on an "as-needed" basis (rescue therapy) in doses up to 4-fold the standard dose. Patients were excluded from these studies if they had evidence of clinically significant cardiovascular disease, a significant bleeding risk, coagulation disorders, ongoing, chronic or recurrent infection, chronic or acute hepatic disease with evidence of ongoing hepatitis C or B, history of renal disease, history of gastrointestinal bleeding or history of malignancy in the last 5 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 the 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 and clinically meaningful improvements in itch and hives symptoms in patients treated with remibrutinib compared to patients given placebo. Results are presented in Table 2 and Figure 1.

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

	REMIX-1		REMIX-2	
	Remibrutinib (N=309)	**Placebo (N=153)**	**Remibrutinib (N=297)**	**Placebo (N=153)**
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)
LS mean (SE) CFB difference 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)
LS mean (SE) CFB difference 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	

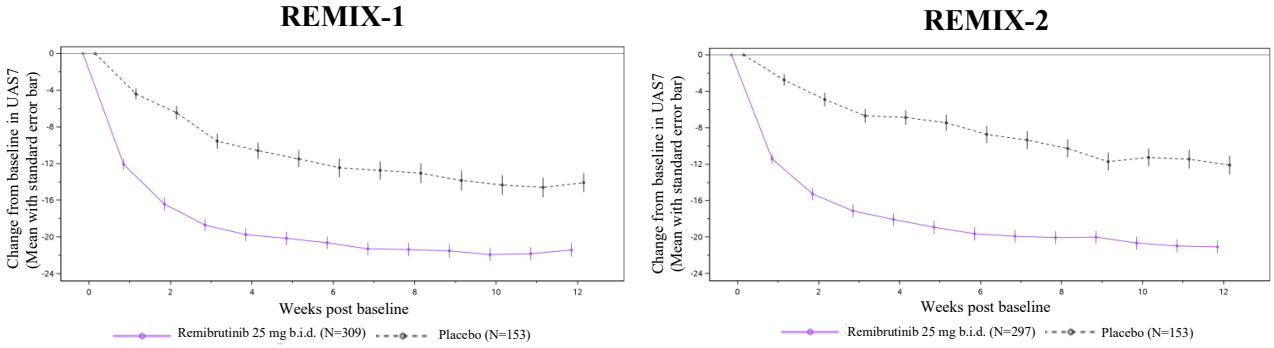
	REMIX-1		REMIX-2	
	Remibrutinib (N=309)	**Placebo (N=153)**	**Remibrutinib (N=297)**	**Placebo (N=153)**
Change from baseline in HSS7 at week 12				
LS mean (SE) CFB	-10.47 (0.401)	-6.86 (0.548)	-10.47 (0.394)	-6.00 (0.531)
LS mean (SE) CFB difference vs placebo	-3.61 (0.635)		-4.47 (0.634)	
95% CI for 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 vs placebo	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 vs placebo	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 vs placebo	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 vs placebo	17.65		18.21	
(95% CI)	9.14, 26.16		9.96, 26.45	
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	
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	

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)

Figure 1 Mean change from baseline in UAS7 up to week 12 in REMIX-1 and REMIX-2 (observed data)



b.i.d. = twice daily

Subgroup analyses demonstrated a consistent treatment benefit with remibrutinib over placebo across subgroups including prior exposure to anti-IgE biologics and total IgE level.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Rhapsido in one or more subsets of the paediatric population in CSU (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Remibrutinib is rapidly absorbed and reaches C_{max} in the blood approximately 1 hour post-dose across all doses studied (0.5 mg to 600 mg). Absorption is considered to be mostly complete (86.9%). 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 remibrutinib. Remibrutinib may be taken with or without food (see section 4.2).

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 pharmacokinetic (PopPK) analysis, the volume of distribution at steady state was 58 litres (central compartment) and 1 180 litres (peripheral compartment).

Biotransformation

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%).

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

Elimination

Remibrutinib has a mean elimination half-life ranging between 1 and 2 hours at steady state. The mean apparent oral clearance at steady state (CLss/F), as determined by the PopPK analysis, is 160 litres/h. Following intravenous administration of 100 mg [^{14}C]-remibrutinib, excretion of radioactivity (remibrutinib and metabolites) was approximately 72.9% of the administered dose in faeces and 27.1% in urine. Renal excretion of unchanged remibrutinib after oral administration was below 1% of the dose.

Linearity/non-linearity

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

Pharmacokinetic/pharmacodynamic relationship(s)

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.

Special populations

PopPK analysis showed that there are no clinically relevant effects of 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 (39 to 162 kg; mean 74.8 kg) on the PK of remibrutinib.

Renal impairment
The effects of renal impairment on remibrutinib pharmacokinetics have not been evaluated in a dedicated clinical study. In a PopPK analysis, no clinically meaningful relationship was observed between renal function tests and remibrutinib pharmacokinetics. In the PopPK analysis, there were 19.3%, 2.2% and 0.1% of subjects with mild, moderate and severe renal impairment, respectively.

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).

Paediatric population
No pharmacokinetic studies were performed with remibrutinib in patients under 18 years of age.

5.3 Preclinical safety data

Remibrutinib inhibited primary antibody responses in rodent pharmacology studies and increased rat tail bleeding time in haemostasis assessments. These observations, which occurred at pharmacologically and clinically relevant exposures, were considered related to effects of remibrutinib on specific B cell and platelet functions, respectively. The non-clinical data revealed no further special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and phototoxicity.

Reproductive toxicity

In embryo-foetal development (EFD) studies in pregnant rabbits, increased foetal external malformations (open/opaque eyes, small jaws, hyperflexion of forelimbs) and maternal toxicity (transiently reduced food consumption and adverse clinical signs) occurred at approximately 141 times the maximum recommended human dose (MRHD) of 25 mg twice daily with a no observed adverse effect level (NOAEL)-based safety margin of 23 times the MRHD of 25 mg twice daily based on AUC. The foetal findings were considered unlikely to be secondary to the maternal toxicity. No effect on EFD was observed in rats, with NOAEL-based safety margin of 126-fold in terms of steady-state AUC compared to human exposure at the MRHD.

In a pre- and postnatal development (PPND) study in rats, remibrutinib induced adverse effects affecting maternal animals (moribundity and clinical signs of toxicity, slightly longer gestation lengths) and offspring up to lactation day 1 (slightly higher mean number of stillborn, dead or missing pups and smaller mean litter size), with NOAEL-based safety margin for maternal animals and offspring of approximately 67 times the MRHD of 25 mg twice daily based on AUC. No adverse effects were noted for the surviving offspring developing into adulthood.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol
Microcrystalline cellulose
Copovidone
Croscarmellose sodium
Sodium stearyl fumarate
Sodium lauryl sulfate

Tablet coating

Polyvinyl alcohol
Macrogol 4000
Talc
Titanium dioxide (E171)
Yellow iron oxide (E172)
Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Rhapsido is supplied in PA/alu/PVC/alu (polyamide/aluminium/polyvinylchloride/aluminium) blisters with aluminium foil backing and is available in packs containing 30, 60 or 180 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2024/001-003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Novartis Pharmaceutical Manufacturing LLC
Verovškova ulica 57
1000 Ljubljana
Slovenia

Novartis Farmaceutica S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rhapsido 25 mg film-coated tablets
remibrutinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 25 mg remibrutinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets
60 film-coated tablets
180 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Do not split, crush or chew.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2024/001	30 film-coated tablets
EU/1/26/2024/002	60 film-coated tablets
EU/1/26/2024/003	180 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rhapsido 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rhapsido 25 mg tablets
remibrutinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Rhapsido 25 mg film-coated tablets
remibrutinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rhapsido is and what it is used for
2. What you need to know before you take Rhapsido
3. How to take Rhapsido
4. Possible side effects
5. How to store Rhapsido
6. Contents of the pack and other information

1. What Rhapsido is and what it is used for

Rhapsido contains the active substance remibrutinib, which belongs to a group of medicines called Bruton's tyrosine kinase (BTK) inhibitors.

Rhapsido is used to treat adults with chronic (long-term) spontaneous urticaria (CSU) when treatment with antihistamines does not work well enough.

In people with CSU, symptoms can happen when the immune system (the body's natural defences) becomes overactive. Certain immune cells switch on a protein called Bruton's tyrosine kinase, which causes hives, itching and/or swelling. Remibrutinib works by blocking BTK which helps stop the immune cells from becoming overactive and reduces inflammation, making CSU symptoms less frequent and less severe.

2. What you need to know before you take Rhapsido

Do not take Rhapsido
- if you are allergic to remibrutinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking Rhapsido:
- if you have or have ever had unusual bruising or bleeding, or are taking any medicines that could increase your risk of bleeding. See section "Other medicines and Rhapsido" below.
- if you have recently had any surgery or are planning to have surgery. Your doctor may ask you to stop taking Rhapsido for a short time before (3 to 7 days) and after (3 to 7 days) your surgery.
- if you have recently had a vaccination or are planning to have a vaccination. Certain types of vaccines (known as live or live-attenuated vaccines) are not recommended to be used during treatment with Rhapsido. If you have had, or are planning to have another type of vaccine (known as a non-live vaccine), your doctor may ask you to stop taking Rhapsido for 1 week before and 2 weeks after the vaccination.
- if you are taking any other medicines as these could interact with Rhapsido. See section "Other medicines and Rhapsido" below.

Children and adolescents
Do not give this medicine to children or adolescents below 18 years of age. It has not been studied in this age group.

Other medicines and Rhapsido
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Rhapsido may make you bleed more easily. This means you should tell your doctor if you take any other medicines or supplements that increase your risk of bleeding (see "Warnings and precautions" above). This includes any of the following:
- medicines used to relieve pain, reduce fever or prevent blood clots, such as acetylsalicylic acid.
- medicines used to treat blood clots, such as clopidogrel.
- medicines used to thin the blood, such as warfarin.

Tell your doctor or pharmacist if you are taking any of the following medicines as they may increase the risk of side effects of Rhapsido, or Rhapsido may increase the risk of side effects of them:
- medicines used to treat HIV infection, such as ritonavir.
- medicines used to treat heart problems, such as digoxin.
- medicines used to treat high cholesterol, such as rosuvastatin.
- medicines used for sedation or sleep disturbances, such as midazolam.

Tell your doctor or pharmacist if you are taking any of the following medicines as they may decrease the effectiveness of Rhapsido:
- medicines used to treat certain types of seizures, such as carbamazepine.

Tell your doctor or pharmacist if you have recently had a vaccination or plan to have a vaccination (see "Warnings and precautions" above).

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Treatment with Rhapsido is not recommended during pregnancy or in women who can become pregnant who are not using effective contraception (birth control). This is because studies in animals have shown that Rhapsido may cause harm to the unborn baby.

Do not breast-feed during treatment with Rhapsido and for one week after stopping treatment, as it is not known if Rhapsido passes into breast milk.

If you are a woman who could become pregnant, you must use an effective method of contraception (birth control) during treatment with Rhapsido and for at least one week after stopping treatment. Ask your doctor about effective methods of contraception.

Driving and using machines
Rhapsido has no or negligible influence on the ability to drive and use machines.

Rhapsido contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially “sodium-free”.

3. How to take Rhapsido

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one 25 mg tablet twice a day, once in the morning and once in the evening.

- Swallow the tablet whole with water.
- Do not split, crush or chew the tablet before swallowing as this may change how much medicine gets into your body.
- To help you remember to take Rhapsido, take it at the same time every day.
- Rhapsido can be taken with or without food.

Rhapsido and surgery
Tell your doctor if you have recently had surgery or plan to have surgery. Your doctor may ask you to stop taking Rhapsido for 3 to 7 days before and 3 to 7 days after any planned medical or surgical procedures.

If you take more Rhapsido than you should
If you take more Rhapsido than you should, talk to a doctor straight away. If you are told to go to the hospital, take the tablet pack and this leaflet with you.

If you forget to take Rhapsido
If you miss a dose then you should take the next dose at your usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Rhapsido
Stopping your treatment with Rhapsido may cause your CSU symptoms to return. Do not stop taking Rhapsido unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

All of the following side effects are mild to moderate.

Very common (may affect more than 1 in 10 people)
- Nose and throat infections (upper respiratory tract infections)

Common (may affect up to 1 in 10 people)
- Herpes virus infection
- Headache
- Bruising
- Tiny red spots under the skin (petechiae)
- Bruising under the skin (contusion)
- A bleeding spot under the skin with blue or purplish patch (ecchymosis)

- Pink or brown urine/blood in the urine (haematuria)
- Feeling sick (nausea)
- Abdominal pain
- Back pain
- Fever (pyrexia)

Uncommon (may affect up to 1 in 100 people)
- Nosebleed (epistaxis)
- Purple or red-brown spots on the skin (purpura)
- A flat, bright red patch in the white of the eye (conjunctival bleeding)
- Bleeding gums (gingival bleeding)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Rhapsido

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister foil after "EXP". The expiry date refers to the last day of that month.

Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rhapsido contains
- The active substance is remibrutinib. Each film-coated tablet contains 25 mg of remibrutinib.
- The other ingredients are mannitol, microcrystalline cellulose, copovidone, croscarmellose sodium, sodium stearyl fumarate, sodium lauryl sulfate. The tablet coating is composed of polyvinyl alcohol, macrogol 4000, talc, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172).

What Rhapsido looks like and contents of the pack
Rhapsido is supplied as 25 mg film-coated tablets. The tablets are light yellow, round and curved. They have "LV" on one side and the company logo on the other side. The tablet diameter is approximately 7 mm.

Rhapsido is supplied in blisters and is available in packs containing 30, 60 or 180 film-coated tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder
Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

Manufacturer
Novartis Pharmaceutical Manufacturing LLC
Verovškova ulica 57
1000 Ljubljana
Slovenia

Novartis Farmaceutica S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Bulgaria EOOD
Тел.: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Danmark
Novartis Healthcare A/S
Tlf.: +45 39 16 84 00

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
SIA Novartis Baltics Eesti filiaal
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Lietuva
SIA Novartis Baltics Lietuvos filialas
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Magyarország
Novartis Hungária Kft.
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Nederland
Novartis Pharma B.V.
Tel: +31 88 04 52 111

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor ehf.
Sími: +354 535 7000

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
SIA Novartis Baltics
Tel: +371 67 887 070

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.