swissmedic

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Swiss Public Assessment Report

Rhapsido

International non-proprietary name:	remibrutinib
Pharmaceutical form:	film-coated tablets
Dosage strength(s):	25 mg
Route(s) of administration:	oral
Marketing authorisation holder:	Novartis Pharma Schweiz AG
Marketing authorisation no.:	70227
Decision and decision date:	approved on 19.06.2026

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AH	Antihistamines
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BTK	Bruton's tyrosine kinase
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CSU	Chronic spontaneous urticaria
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HCP	Healthcare professional
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
V_{SS}	Volume of distribution at steady state

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

New active substance status
The applicant requested new active substance status for remibrutinib in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

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

2.2.2 Approved indication

Rhapsido is indicated as an add-on therapy for the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment.

2.2.3 Requested dosage

Summary of the requested standard dosage:

- Usual dosage: 25 mg orally b.i.d.
- Interruption of treatment: Depending on the type of procedure and the risk of bleeding, discontinue use 3 to 7 days before and 3 to 7 days after surgery.
- Patients with renal impairment: No dose adjustment necessary.
- Patients with hepatic impairment: No dose adjustment necessary.
- Paediatric patients (under 18 years of age): Safety and efficacy have not been established.
- Elderly patients (65 years or older): No relevant pharmacokinetic differences observed compared to the total population. Therefore no dose adjustment necessary.
- Route of administration: Taken orally. Can be taken with or without food. To be swallowed with water.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	14 May 2025
Formal control completed	20 May 2025
List of Questions (LoQ)	28 August 2025
Response to LoQ	20 November 2025
Preliminary decision	18 February 2026
Response to preliminary decision	19 April 2026
Final decision	19 June 2026
Decision	approval

3 Medical context

Chronic spontaneous urticaria (CSU) is an unpredictable disease of the skin characterised by the spontaneous and recurrent appearance of itchy weals (hives), angioedema, or both. The weals are intensely pruritic, resolve in < 24 hours and tend to recur on a daily basis [Yosipovitch et al 2023]. CSU lasts for at least 6 weeks [Zuberbier et al 2022] but often takes several years to resolve and may even persist over decades [Maurer & Grabbe 2008, Maurer et al 2011]. Spontaneous remission is seen in 30–50% of cases [Saini S: CSU: Clinical manifestations, diagnosis, pathogenesis, and natural history. In: UpToDate, Connor RF (Ed), Wolters Kluwer. Accessed on 14.08.2026]. The prevalence of diagnosed CSU in 5 European countries (France, Germany, Italy, Spain, and the UK) is 0.92% (95% CI: 0.92%–0.92%) [Balp et. Al. 2025]. The disease burden is substantial for CSU patients as it is extremely stressful due to the unpredictable nature of exacerbations. Available data indicate that urticaria markedly affects both objective functioning and subjective well-being. O'Donnell et al. showed that health status scores in CSU patients are comparable to those reported by patients with coronary artery disease. Furthermore, both health status and subjective satisfaction in patients with CSU are lower than in patients with respiratory allergy. [International EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Zuberbier et al, 2022; Baiardini et al, 2003].

The recommended first-line treatment for patients with CSU is second-generation H1-antihistamines (H1-AHs) including up-titration to up to 4-fold the approved dose (i.e. off-label). A meta-analysis of studies showed that approx. 60% of patients with CSU treated with second-generation H1-AHs remained uncontrolled [Guillén-Aguinaga et al 2016]. Omalizumab, a licensed anti-IgE monoclonal antibody for the SC treatment of CSU in patients who remain symptomatic despite H1-AH treatment, is recommended as a second-line add-on treatment. Patient response varies, with many patients on omalizumab 300 mg failing to achieve complete response [Saini, Kaplan 2018] and some patients requiring higher than approved doses of omalizumab. In non-responders to these therapies, off-label use of ciclosporin or glucocorticoids is recommended. [International EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Zuberbier et al, 2022]

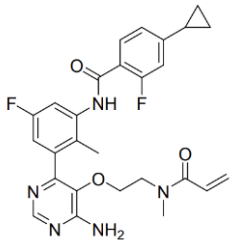
Given the substantial impact of CSU on patients' quality of life and the limitations of the current therapies, there is a high unmet medical need for alternative second-line oral treatments for patients who remain symptomatic despite H1-AH treatment.

Remibrutinib is a new selective oral BTK (Bruton's tyrosine kinase) inhibitor.
Other BTK inhibitors are approved for oncological indications.

4 Quality aspects

4.1 Drug substance

INN: remibrutinib
Chemical name: N-(3-{6-Amino-5-[2-(N-methylprop-2-enamido)ethoxy]pyrimidin-4-yl}-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide
Molecular formula: $C_{27}H_{27}F_2N_5O_3$
Molecular mass: 507.54
Molecular structure:



Physicochemical properties: Remibrutinib is a white to pale yellow powder. Remibrutinib is not chiral.

Synthesis: The drug substance is manufactured by multiple step chemical synthesis. The synthesis of the drug substance and the necessary in-process controls are described in detail.

Specification: In order to ensure consistent quality of the drug substance, the specifications include all relevant test parameters as recommended by the relevant ICH guidelines.

Stability: Appropriate stability data have been generated, resulting in a suitable retest period.

4.2 Drug product

Description and composition: Remibrutinib 25 mg tablets are immediate-release film-coated tablets for oral administration. They are round, curved without score, light yellow, debossed with ‘LV’ on one side and the ‘Novartis’ symbol on the other side.

Manufacture: Remibrutinib film-coated tablets are manufactured by a non-standard process consisting of wet media milling, spray granulation, blending, compression into tablets, and film coating. Adequate process parameters and in-process controls are defined in order to ensure consistent quality of the tablets.

Specification: Adequate tests and criteria at release and during shelf-life are established for the control of the finished product. The test methods applied are adequately validated according to the recommendations of the current scientific guidelines.

Stability: Appropriate stability data have been generated in the packaging material intended for commercial use and according to the relevant international guidelines.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

5.1 Pharmacology

Remibrutinib is a covalent Bruton's tyrosine kinase (BTK) inhibitor. In enzymatic assays, remibrutinib potently inhibited BTK with IC_{50} values in the low nanomolar range. Selectivity was demonstrated in comparison to related kinases, showing at least 17-fold higher IC_{50} values (TEC protein tyrosine kinase: 124 nM) compared to unbound plasma C_{max} at the recommended clinical dose. In cell-based systems, remibrutinib inhibited functional readouts of BTK-dependent signalling pathways. Remibrutinib inhibited FcεRI-mediated degranulation in primary human mast cells derived from skin (IC_{50} of 17.2 nM) and primary human blood basophils (IC_{50} of 71.8 nM). The effect on FcγR-signalling was investigated in the human monocytic cell line THP1. Remibrutinib inhibited IL8 secretion with an IC_{50} of 2.5 nM. Cellular B cell antigen receptor (BCR) inhibition was shown in the human Ramos lymphoma cell line (IC_{50} of 11 nM) and primary B cells from humans (IC_{50} values of 7-18.3 nM) and rodents (IC_{50} values of 1.2-1.8 nM). T cell antigen receptor signalling in activated T cells was not inhibited.

The rate of BTK recovery was characterised in rats after single oral doses. BTK turnover is much longer in rat blood (approximate half-life: 87 hours) than in the spleen (approximate half-life: 5 hours).

The applicant demonstrated efficacy in disease rodent models. Remibrutinib significantly inhibited skin swelling in the acute reverse passive Arthus (RPA) model in mice at ≥ 30 mg/kg. In the mouse model of passive cutaneous anaphylaxis (PCA), remibrutinib inhibited the skin anaphylaxis reaction in the low dose IgE setting at ≥ 3 mg/kg. Proof of concept was also demonstrated in an SRBC-specific haemolytic plaque formation assay in rats, which is a model for the inhibition of B cell-dependent antibody formation. Remibrutinib decreased the number of anti-SRBC secreting cells significantly at ≥ 0.3 mg/kg. In conclusion, the mode of action of remibrutinib as a BTK inhibitor has been sufficiently characterised in pharmacology studies.

Remibrutinib did not show any off-target activity in a secondary pharmacology screen except for 89% binding inhibition of the human cannabinoid CB2 receptor (1370-fold the unbound C_{max} at the recommended clinical dose). In a functional follow up, no agonism or antagonism towards the human CB2 receptor were shown. Remibrutinib inhibited VMAT-2 *in vitro* with an IC_{50} value of 13 µM (1780-fold the unbound C_{max} at therapeutic dose). Another *in vitro* study on secondary pharmacology showed inhibition of platelet function in platelet-rich plasma prepared from fresh human blood.

The applicant conducted safety pharmacology studies to investigate potential effects on the cardiovascular, respiratory, and central nervous systems. Remibrutinib inhibited hERG potassium channel current at an IC_{50} of 1.4 µM, corresponding to 192-fold the unbound plasma C_{max} at the recommended clinical dose. There were no ECG changes or effects on heart rate in dogs in a GLP single-dose study up to 450 mg/kg. In a 3-day non-GLP study, cardiovascular investigations were performed in dogs at 400 mg/kg/day and showed a slight and reversible QTc increase (46-fold the unbound plasma C_{max} at the recommended clinical dose). No cardiovascular effects were observed in chronic toxicity studies. No relevant effects were observed in the central nervous or respiratory system.

5.2 Pharmacokinetics

The PK profile of remibrutinib was characterised after single intravenous and oral administration in mice, rats, and dogs as well as repeated oral administration in rats and dogs.

Absorption of remibrutinib after oral administration was generally rapid in animals, with T_{max} within 0.25-2 hours, which is comparable to human absorption (T_{max}: approximately 1 hour). The extent of absorption was lower in animals (37-78% in rats and dogs) than in humans (75%). Oral bioavailability

of remibrutinib in PK studies was low in mice, rats, and dogs, indicating a significant first pass effect in animals. Mean V_{ss} was moderate.

In quantitative whole-body autoradiography studies with ^{14}C- or ^{3}H-labelled remibrutinib in rats, radioactivity was quickly and widely distributed throughout the body. High concentrations of radioactivity were found in the gastrointestinal tract, liver, and kidney. No radioactivity was detected in the brain, spinal cord, white fat, and lens of the eye. Remibrutinib distributed into melanin-containing structures of the eye and skin. Binding was at least partially reversible. No ophthalmologic or skin effects were observed in the toxicity studies in rats and dogs.

Some covalent binding of remibrutinib to proteins was shown in blood. In plasma, covalent binding was 60-70% in rat and dog and less than 10% in human. Remibrutinib bound covalently to proteins in HLM and human hepatocytes. Plasma protein binding was high in rats, dogs and humans, with unbound fractions of 10% in rats, 7% in dogs, and 5% in humans. Blood-to-plasma ratios indicated a preferential location in plasma in all species. Some placental transfer was shown in pregnant rabbits after oral dosing, and the potential for fetal exposure cannot be excluded.

Metabolism of remibrutinib was investigated *in vitro* in human liver microsomes and in mouse, rat, dog, and human hepatocytes. N-demethylation, O-dealkylation, and modification of the double bond in the N-methylacrylamide moiety were identified as major pathways. The major metabolite M24 in human hepatocytes was also represented in dog and mouse hepatocytes. All human identified metabolites were detected in rat and/or dog blood. The diastereomers M68a and M68b are prominent human metabolites that together represented 11.2% of the blood [^{14}C]-$AUC_{0\text{-}24h}$ in a clinical study. They are not expected to undergo chiral conversion. The major route of excretion in nonclinical species and human was faecal, with minor renal excretion.

5.3 Toxicology

The nonclinical safety profile of remibrutinib was characterised in rats (up to 26 weeks) and dogs (up to 39 weeks). Rats and dogs were pharmacologically relevant species. The oral route of administration as well as the duration of the studies in rodents and non-rodents support the clinical use.

Generally, remibrutinib was well tolerated up to and including the highest dose tested. Target organs of toxicity were the lymphoid organs, liver, and haematopoietic and immune system in both species, and the pancreas in rats. Findings in the lymphoid organs consisted mainly of decreased development of germinal centres in mandibular and mesenteric lymph nodes, as well as gut-associated lymphoid tissues. They were considered pharmacology related and not adverse. Remibrutinib inhibited platelet aggregation and prolonged bleeding time in animals at pharmacologically relevant exposure. The effect was not considered adverse in dogs in the context of a mucosal bleeding assessment but was related to mortality in rats after vascular injury in the context of a tail bleeding assessment. Serious bleeding events are considered an important potential risk in the RMP. A NOAEL was not identified in the 26-week rat study due to pancreas findings that were considered rat specific. At the dose level of 300 mg/kg/day, considered relevant for human risk assessment, exposure margins were 15 to 79-fold human AUC at therapeutic dose (in males and females). At the NOAEL in the 39-week study in dogs, exposure was 77 to 146-fold (in males and females) above human AUC at therapeutic dose.

Remibrutinib was not genotoxic or carcinogenic in rats and mice.

Remibrutinib did not impair male or female fertility in a fertility and early embryonic development study conducted in male and female rats with oral administration at doses up to 1000 mg/kg/day. In an embryo-fetal development study in rats with oral administration of doses up to 1000 mg/kg/day remibrutinib, no effects on pregnancy or embryo-fetal development were observed. In rabbits, a dose level of 450 mg/kg/day induced mortality in the pivotal study. At 300 mg/kg/day, external fetal malformations were noted. At NOAEL, $AUC_{0\text{-}24h}$ corresponded to 23-fold the human exposure.

Remibrutinib showed no phototoxicity potential *in vitro*. There were no concerns related to excipients or impurities. All nonclinical data that are relevant for safety are included in the nonclinical part of the safety specification of the RMP. Based on the ERA, use of remibrutinib is not expected to pose a risk to the environment.

5.4 Nonclinical conclusions

In conclusion, the pharmaco-toxicological profile of remibrutinib was well characterised. The application is approvable from the nonclinical perspective. The relevant information has been included in the Information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

The proposed posology for treatment of chronic spontaneous urticaria (CSU) is 25 mg remibrutinib b.i.d. p.o. with or without food, given as a film-coated tablet.
The clinical pharmacology of remibrutinib is well-characterised and the available data, both PK/PD and exposure/response, support the selection of 25 mg b.i.d. The upper and lower bound of the therapeutic window have not been clearly defined, despite higher exposures being tolerated such as 100 mg b.i.d. up to 68 weeks, corresponding to a steady-state AUC ratio of 4.18, compared to 25 mg b.i.d. and a C_{max} ratio of 3.27. In consequence, considering the bleeding risk and other class effects of BTKi, use in patients with severe hepatic impairment is not recommended. Similarly, coadministration with strong CYP3A4 inhibitors as well as strong and moderate CYP3A4 inducers is not recommended.

6.2 Dose finding and dose recommendation

A dedicated Phase 2b dose-finding study (A2201) was conducted as multi-centre, randomised, double-blind, placebo-controlled trial to investigate the efficacy, safety, and tolerability of remibrutinib in adult CSU patients inadequately controlled by H1-antihistamines.
Six verum dose regimens were compared to placebo: 10 mg q.d. (n = 44), 35 mg q.d. (n = 44), 100 mg q.d. (n = 47), 10 mg b.i.d. (n = 44), 25 mg b.i.d. (n = 44), 100 mg b.i.d. (n = 45) vs. placebo (n = 43).
Maximum efficacy in terms of the UAS7 score (reduction from baseline, UAS7=0, and UAS<6) was achieved with the remibrutinib 25 mg b.i.d. dosing.
The higher dosing regimen (100 mg b.i.d.) did not further increase the maximum efficacy, and neither the lower remibrutinib b.i.d. dose (10 mg b.i.d.) nor the q.d. dosing achieved maximum efficacy.
Based on the safety results, there was no dose-dependent safety signal which would prevent the selection of a remibrutinib dose or further clinical development of the drug.
Hence, the 25 mg b.i.d. dose regimen was chosen for the Phase 3 studies, which seems acceptable.

6.3 Efficacy

Two identically designed pivotal Phase 3 studies, REMIX-1 (A2301) and REMIX-2 (A2302), were submitted. Both were multicentre, randomised (2:1), double-blind, placebo-controlled studies of remibrutinib to investigate efficacy, safety, and tolerability in adult patients with moderate to severe CSU, inadequately controlled by H1-antihistamines.
The primary endpoint was to be assessed at Week 12; the double-blind period lasted until Week 24, followed by open-label remibrutinib treatment for a further 28 weeks until Week 52.

The study participants had to meet the following key inclusion criteria: a diagnosis of CSU with a disease duration of ≥ 6 months prior to screening, inadequately controlled defined as the presence of itch and hives for ≥ 6 consecutive weeks prior to screening despite the use of second-generation H1-AHs during this period. Patients had to have urticaria of at least moderate activity and mild disease severity in terms of itch and hives (see Appendix). Suffering from angioedema (AAS) was not required for study participation.

All patients were randomised 2:1 to either remibrutinib 25 mg b.i.d. treatment or placebo (REMIX-1: n=313 versus n=157; REMIX-2: n=300 versus n=155). At Week 24, the patients in the placebo arm were switched to open-label remibrutinib 25 mg b.i.d.

Remibrutinib was an add-on treatment to a stable, locally standard approved dose of a second-generation H1-antihistamine (H1-AH) “background therapy” throughout the entire study.

The primary objective was to demonstrate that remibrutinib (25 mg b.i.d.) is superior to placebo in patients with CSU, with the primary endpoint being defined as absolute change from baseline in the Weekly Urticaria Activity Score UAS7 at Week 12. The most important key secondary endpoints were achievement of disease control at Week 12 and achievement of complete absence of itch and hives at Week 12.

The baseline demographic and disease characteristics are described in the Information for healthcare professionals.

Week 12 efficacy results

The primary as well as all (key) secondary endpoints were met. Both studies demonstrated superiority of remibrutinib over placebo at Week 12.
Regarding the primary endpoint, a higher reduction of urticaria activity (UAS7) was seen after 12 weeks of treatment with remibrutinib compared to placebo; the treatment difference versus placebo was of borderline clinical relevance (<10), but statistically significant and consistent across both the REMIX-1 and -2 studies (REMIX-1: -6.22 (95% CI: -8.45, -4.00), REMIX-2: -7.68 (95% CI: -9.91, -5.46;). Predefined sensitivity analyses supported the results of the primary endpoint analysis.
Post-hoc analyses showed that clinically relevant higher proportions of patients treated with remibrutinib compared to placebo reached at least the minimal important difference (MID, as defined by Mathias et al. 2012 and 2015) for the urticaria activity, itch severity and hive severity score changes from baseline at Week 12 in both pivotal studies, REMIX-1 and REMIX-2.
The most ambitious key secondary endpoint, absence of itch and hives (UAS7 = 0) at Week 12, was achieved by 31.1% and 27.9% of REMIX-1 and -2 patients, respectively, with a treatment difference versus placebo of 20.55% and 21.60%, respectively, which is clinically relevant.
Another important key secondary endpoint, disease activity control (UAS7 ≤ 6) at Week 12, was achieved by 49.8% and 46.8% of REMIX-1 and -2 patients, respectively, with a treatment difference versus placebo of 25.44% and 27.61%, respectively, which is also clinically relevant.

Week 52 efficacy results

For patients in the remibrutinib arm, the treatment response (UAS7) at Week 12 was sustained up to Week 52. For patients in the placebo arm, there was an improvement in the treatment response (UAS7) after transitioning to remibrutinib in Week 24 until Week 52, similarly to patients initially randomised to remibrutinib.

In summary, both pivotal studies showed a small but consistent statistically significant treatment effect across all primary and the (key) secondary endpoints, and consequently support the requested indication and posology in terms of efficacy.

Two clinical studies in CSU patients with remibrutinib 25 mg b.i.d. are ongoing:

- Study A2303B, a Phase 3 extension study, is an ongoing multicentre, double-blind, placebo-controlled, randomised withdrawal and open-label *extension* study followed by long-term open-label treatment cycles to assess the efficacy, safety, and tolerability of remibrutinib in adult CSU patients who completed 1 of the pivotal Phase 3 studies, REMIX 1 or 2. Study treatment consists – depending on study phase – of blinded or open-label remibrutinib 25 mg b.i.d..
- Study A2304 is an ongoing global, multicentre, randomised, double-blind, double-dummy, *active*-controlled, parallel group, Phase 3b study to assess the efficacy, safety, and tolerability of remibrutinib 25 mg b.i.d. in comparison to omalizumab 300 mg every 4 weeks (the only other approved second-line treatment) over 52 weeks in adult patients with CSU inadequately controlled by second generation H1-antihistamines. An open-label 52-week optional extension follows to assess long term efficacy, safety, and tolerability of remibrutinib 25 mg b.i.d.

As a post-approval requirement, the final CSRs of these studies must be submitted as soon as available.

6.4 Safety

Safety data for remibrutinib were evaluated in 2 safety pools:

- Pool 1 included all safety data from the 2 pivotal Phase 3 studies, REMIX-1 (A2301) and REMIX-2 (A2302). The main purpose of Pool 1 was to examine the dose-specific effects of remibrutinib 25 mg b.i.d. vs. placebo in the 24-week placebo-controlled period. In addition, analyses based on the entire study period of Pool 1 provided safety data until Week 52 as well as safety data after placebo patients had switched to remibrutinib 25 mg b.i.d. at Week 24.
- Pool 2 included all safety data from the 2 pivotal Phase 3 studies, REMIX-1 (A2301) and REMIX-2 (A2302), plus the supportive Phase 2b dose ranging study A2201 and its extension A2201E1, plus a supportive Phase 3 study A1301 in Japanese patients. The main purpose of Pool 2 was to estimate the dose average (dose pooled) AE frequency in all remibrutinib-treated patients, regardless of dose (Remibrutinib-Any-Dose-Group) and AE frequency in patients treated with remibrutinib 25 mg b.i.d. with maximum precision based on all available data, and to maximise the sample size and the cumulative exposure time for remibrutinib overall or remibrutinib 25 mg b.i.d. for the assessment of rare events.

The largest body of evidence for exposure duration comes from Pool 2 (comprising the 5 Phase 2 and 3 clinical studies in patients with CSU: A2301, A2302, A2201, A2201E1, and A1301): The safety data from these 5 studies come from 1234 adult patients with CSU, treated with remibrutinib at doses ranging from 10 mg q.d. to 100 mg b.i.d., including 1172 patients treated with remibrutinib at 25 mg b.i.d. or 100 mg b.i.d.
For the Any-Remibrutinib-25.mg b.i.d.-Group in Pool 2, the mean duration of exposure was 39.93 weeks and the median duration of exposure was 52.00 weeks (range 0.1 to 60.6 weeks), with a cumulative exposure of 751.47 patient years. For the Remibrutinib-Any-Dose-Group in Pool 2, the mean duration of exposure was 41.10 weeks and the median duration of exposure was 52.00 weeks (range 0.1 to 69.9 weeks), with a cumulative exposure of 971.94 patient-years.

No deaths were reported in clinical studies.

All SAEs by PT from the pooled pivotal REMIX-1 and -2 studies (Pool 1) were single cases and considered not related to remibrutinib. No pattern was recognised, nor was an increase observed in the exposure-adjusted incidence rate (EAIR) for patients with SAEs during the entire 52-week study period compared with the 24-week placebo-controlled period in Pool 1.
Similarly, most SAEs in the Remibrutinib-Any-Dose-Group and in the Any-Remibrutinib-25.mg b.i.d.-Group (Pool 2) were single cases and no pattern was recognised.
Notably, in the Phase 2b study A2201E1, under treatment with 4-fold the approved dose of remibrutinib (100 mg b.i.d.), 1 notable bleeding SAE of moderate melaena occurred due to bariatric surgery but was considered not related to study treatment.

The most common AEs, which occurred more frequently in the remibrutinib versus the placebo treatment group of the pooled pivotal REMIX-1 and -2 studies (Pool 1), were petechiae (3.8% vs 0.3%) and nasopharyngitis (6.6% versus 4.6%) during the 24-week placebo-controlled period. During the total 52-week study period of Pool 1, the most frequently reported AEs in ≥ 3% of patients treated with remibrutinib since the start of the study were mainly infections, headache, bleeding events, CSU exacerbation, and GI events: COVID-19 (15.5%), nasopharyngitis (9.1%), headache (7.8%), upper respiratory tract infection (5.6%), petechiae (4.0%), urinary tract infection (4.6%), urticaria (3.3%), cough (3.1%), nausea (3.1%), and influenza (3.0%).

Those AEs which were identified by the applicant as related to remibrutinib are listed as ADRs in the Information for healthcare professionals. During clinical assessment, further ADRs (herpes virus infection, headache, haematuria, nausea, abdominal pain, back pain, and pyrexia) were identified and also included in the list of ADRs in the Information for healthcare professionals.

Bleeding, infections, cytopenia, cardiac arrythmias, and hypertension were defined as AESIs; these were derived from clinical trials with other BTK inhibitors which are approved for oncological indications. In addition, liver toxicity, and malignant diseases are also known ADRs of other BTK inhibitors approved for oncological indications.
In the clinical studies with remibrutinib in CSU patients, these AESIs have generally manifested with lower intensity, lower frequency, or not at all, or in some cases a causal relationship with remibrutinib could not be established (e.g. for malignancies). A detailed description of the findings from the clinical studies with remibrutinib regarding these AESIs can be found in the Information for healthcare professionals. Furthermore, a warning about the bleeding risk was included in the Information for healthcare professionals.
Notably, potential risk populations for these AESIs were excluded from the clinical studies with remibrutinib; accordingly, the risk of these AESIs in these patients can not adequately be assessed. and remibrutinib should be administered only with caution.

Any (potential) risks will be further followed up in the 2 above-mentioned ongoing clinical studies in CSU patients with remibrutinib 25 mg b.i.d. that will be submitted as a post-approval requirement.

6.5 Final clinical benefit-risk assessment

CSU is an unpredictable disease of the skin characterised by the spontaneous and recurrent appearance of itchy weals (hives), angioedema, or both. The weals are intensely pruritic. CSU often takes several years to resolve and may even persist over decades.

The disease burden is substantial for CSU patients as it is extremely stressful due to the unpredictable nature of exacerbations.

Given the substantial impact of CSU on patients' quality of life and the limitations of the current therapies, there is a high unmet medical need for alternative second-line oral treatments for patients who remain symptomatic despite H1-AH treatment.

Based on the totality of the available efficacy data from the clinical studies in adult patients with CSU who were inadequately controlled by second-generation H1-antihistamines, remibrutinib 25 mg b.i.d. shows a modest treatment effect which is consistent across the Phase 2 and 3 studies, across all primary and key secondary and other secondary efficacy endpoints, as well as post-hoc responder analyses. The safety of remibrutinib 25 mg b.i.d. was acceptable with the inclusion of several risk mitigation measures in the Information for healthcare professionals.

Overall, the benefit/risk ratio for remibrutinib was assessed as positive for adult patients with CSU who are inadequately controlled by second-generation H1-antihistamines.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Rhapsido was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See “Adverse effects” for information on reporting adverse effects.

Rhapsido

Composition

Active substances

Remibrutinib.

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).
One film-coated tablet contains a maximum of 0.84 mg sodium.

Pharmaceutical form and quantity of active substance per unit

Each film-coated tablet contains 25 mg remibrutinib.
Light yellow, round, curved film-coated tablet with a diameter of 7 mm, debossed with “LV” on one side and the “Novartis” logo on the other side.

Indications/Potential uses

Chronic spontaneous urticaria (CSU)
Rhapsido is indicated as an add-on therapy for the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment.

Dosage/Administration

Usual dosage
The recommended dosage of Rhapsido is 25 mg orally twice daily
If a patient misses a dose or doses of Rhapsido, the patient should be instructed to take the next dose at the regularly scheduled time. Extra doses of Rhapsido should not be taken to make up for the missed dose or doses.

Interruption of treatment

Consideration should be given to interrupting 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 “Adverse effects” and “Interactions”).

Patients with renal impairment

No dose adjustment of Rhapsido is required in patients with renal impairment. There are very limited data available in patients with severe renal impairment (see “Pharmacokinetics”).

Patients with hepatic impairment

Rhapsido is not recommended for use in patients with severe hepatic impairment. No dose adjustment is necessary in patients with mild or moderate hepatic impairment (see “Pharmacokinetics”).

Paediatric patients (aged under 18 years)

The safety and efficacy of Rhapsido in paediatric patients have not been established.

Elderly patients (aged 65 years or over)

No relevant pharmacokinetic differences have been observed in elderly patients (aged ≥65 years) compared to the overall population. Therefore, no dose adjustment is required in patients aged 65 years and over (see “Properties/Actions”).

Method of administration

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

Contraindications

Hypersensitivity to the active substance or any of the excipients listed under “Composition”.

Warnings and precautions

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 “Adverse reactions”).

Patients taking 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 “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 of the bleeding, 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 "Dosage/Administration").

Live 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 "Interactions").

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 "Interactions").

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 "Interactions").

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 "Interactions").

Populations not studied

Potential at-risk populations were excluded from the clinical trials with remibrutinib and therefore should be treated with caution, as adverse pharmacologic effects known from other Bruton's tyrosine kinase (BTK) inhibitors used in oncological diseases cannot be excluded (see "Description of selected adverse drug reactions"):

- Patients with a significant risk of bleeding or coagulation disorders, with a history of gastrointestinal bleeding or an INR >1.5, with antiplatelet therapy (except acetylsalicylic acid up to 100 mg/day or clopidogrel up to 75 mg/day), with dual antiplatelet therapy (e.g. acetylsalicylic acid + clopidogrel), or with anticoagulant medication (e.g. warfarin or other vitamin K antagonists as well as new oral anticoagulants).
- Patients with clinically significant cardiovascular diseases (e.g. status post myocardial infarction, unstable angina pectoris, NYHA Class III/IV left ventricular failure, arrhythmias and uncontrolled hypertension).
- Patients with the following haematological parameters (cytopenias): Haemoglobin: <10 g/dl, Platelets: <100,000/mm^3, Leukocytes: <3,000/mm^3, Neutrophils: <1,500/mm^3.
- Patients with immunodeficiency
- Patients with a history of or current liver disease, including but not limited to acute or chronic hepatitis, liver cirrhosis or liver failure, or aspartate aminotransferase (AST)/alanine

aminotransferase (ALT) levels greater than 1.5 times the upper limit of normal (ULN) or an International Normalised Ratio (INR) greater than 1.5.

- Patients with a history of renal disease, a creatinine >1.5 times ULN or estimated Glomerular Filtration Rate (eGFR) <45 ml/min (using the Cockcroft-Gault equation) at screening
- Patients with malignant diseases (other than localised basal cell carcinoma of the skin or in situ cervical cancer) within the last 5 years.

Sodium

This medicinal product contains less than 1 mmol (23 mg) of sodium per tablet, making it practically "sodium-free".

Interactions

Effect of other medicinal products on remibrutinib

CYP3A4 inhibitors

The concomitant use of remibrutinib with strong CYP3A4 inhibitors is not recommended (see "Warnings and precautions"). Concomitant use of ritonavir, a potent CYP3A4/P-gp inhibitor, led to a 4.27-fold increase in the area under the curve (AUC) and a 3.32-fold increase in the C_{max} of remibrutinib

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

CYP3A4 inducers

Co-administration of remibrutinib with strong or moderate CYP3A4 inducers must be avoided (see "Warnings and precautions"). Co-administration of carbamazepine (strong to moderate CYP3A4 inducer) decreased remibrutinib blood exposure by 0.26-fold for C_{max} and by 0.23-fold in the AUC.

In vitro evaluation of the drug interaction potential

In vitro data showed that remibrutinib is a P-gp substrate. The *in vitro* CYP metabolism is predominantly driven by CYP3A4. Remibrutinib is not a substrate of OATP1B1 and 1B3, or BCRP.

Effects of remibrutinib on other medicinal products

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 1.45-fold increase in the AUC and a 2.08-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 1.65-fold increase in the AUC and a 1.56-fold increase in the C_{max} of rosuvastatin.

CYP3A4 substrates

Concomitant administration of the CYP3A4 substrate midazolam with remibrutinib 100 mg twice daily increased the C_{max} and AUC of midazolam by 1.27-fold and 1.43-fold, respectively. At a remibrutinib dose of 25 mg twice daily, the increase in C_{max} and AUC of midazolam is expected to be smaller and there is no risk of drug interaction for CYP3A4 substrates.

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-fold and 1.36-fold increase in C_{max} and 1.16-fold and 1.39-fold increase in the 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.
The vaccination immune response of non-live vaccines can be reduced with concomitant remibrutinib treatment. Therefore, the use of non-live vaccines with remibrutinib should be considered on a case-by-case basis.

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. Individual use of the antiplatelet agents such as acetylsalicylic acid (up to 100 mg daily) or clopidogrel (up to 75 mg daily) was allowed in the remibrutinib clinical studies, however dual antiplatelet therapy (acetylsalicylic acid and clopidogrel) was prohibited. The risks and benefits of co-administration of antithrombotic agents with remibrutinib must be considered (see “Dosage/Administration” and “Adverse effects”).

In vitro evaluation of drug interaction potential

In vitro, at physiologically relevant concentrations such as those achieved with 25 mg remibrutinib twice daily (BID), remibrutinib showed no inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, and no induction of CYP1A2, CYP2B6, and CYP2C9. In addition, remibrutinib showed no inhibition of BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, and MATE2-K.

Pregnancy/Breast-feeding

Treatment of women of childbearing potential/contraception

Women of childbearing potential should consider using an effective contraception method during Rhapsido treatment and for at least 1 week after the last dose.

Pregnancy

There are limited data from the use of Rhapsido in pregnant women. Animal studies have shown embryo-foetal development toxicity at high exposures (see “Preclinical Data”). Rhapsido is not recommended during pregnancy and in women of childbearing potential not using contraception. The patient should be advised that remibrutinib may potentially cause foetal harm when Rhapsido is administered during pregnancy or if the patient becomes pregnant while taking Rhapsido.

Breast-feeding

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 breast-fed child or on milk production. Because of the potential for adverse drug reactions in breast-fed children, women are to be advised not to breast-feed during treatment with Rhapsido and for 1 week after the last dose.

Fertility

There are no data on the effect of Rhapsido on human fertility. Animal studies have shown no impairment of male or female fertility.

Effects on ability to drive and use machines

No relevant studies have been performed.

Adverse effects

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 25 mg Rhapsido 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 in which all patients received 25 mg Rhapsido 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 use (frequency ≥5%) was upper respiratory tract infections (14.7%) and bleeding (7.8%). All adverse drug reactions were mild to moderate. No severe adverse drug reactions were reported.

Tabulated summary of adverse drug reactions from clinical studies

Adverse drug reactions from clinical studies (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are listed by frequency, with the most frequent adverse drug reactions first. In addition, the corresponding frequency category for each

adverse drug reaction 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 infection[1]	89 (14.7%)	36 (11.8%)	Very common
Herpes virus infections[2]	6 (1.0%)	1 (0.3%)	Common
Nervous system disorders			
Headache	41 (6.8 %)	19 (6.2%)	Common
Skin and subcutaneous tissue disorders			
Petechiae	23 (3.8%)	1 (0.3%)	Common
Contusion[3]	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			
Haematuria	6 (1.0%)	1 (0.3%)	Common
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
Gastrointestinal disorders			
Nausea	18 (3.0%)	5 (1.6%)	Common
Abdominal pain	6 (1.0%)	3 (1.0%)	Common
Musculoskeletal and connective tissue disorders			
Back pain	13 (2.1%)	2 (0.7%)	Common
General disorders and administration site complaints			
Pyrexia	12 (2.0%)	4 (1.3%)	Common

[1]Includes upper respiratory tract infection, acute sinusitis, bacterial tonsillitis, bacterial upper respiratory tract infection, chronic sinusitis, H1N1 influenza, influenza, laryngitis, nasopharyngitis, pharyngitis, streptococcal pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, viral upper respiratory tract infection.
[2]Includes herpes simplex, herpes zoster, oral herpes
[3]Includes contusion, haematoma, increased tendency to bruise

The safety profile of Rhapsido in patients treated for up to 52 weeks was consistent with that observed up to 24 weeks in the pooled REMIX-1 and REMIX-2 studies.
Experience with remibrutinib treatment in CSU patients longer than 1 year is very limited.

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 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 required treatment interruption. None of these events occurred in the placebo group (see “Dosage/Administration” and “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 mucocutaneous bleeding events up to 52 weeks were mild to moderate; none were severe. No additional treatment interruptions and only one treatment discontinuation were reported during Rhapsido use.
Patients with an increased risk of bleeding were excluded from the clinical trials with remibrutinib in CSU. The “Warnings and precautions/bleeding” and “Populations not studied” should also be noted.

The following side effects, some severe or serious including fatal, have been observed with other BTK inhibitors in the treatment of oncological diseases. Patients who had an increased risk of these side effects due to a pre-existing condition were excluded from the clinical trials (see “Warnings and precautions” and “Populations not studied”):

- *Infections as well as reactivation of the hepatitis B virus and opportunistic infections*.
  In clinical trials with remibrutinib in CSU, infections were observed in patients treated with remibrutinib that were mostly mild to moderate. No cases of hepatitis B virus reactivation or opportunistic infections were observed.
- *Cytopenias including neutropenias, anaemias or thrombocytopenias of severity grade 3 and 4*.
  In clinical trials with remibrutinib in CSU, slightly more patients treated with remibrutinib had cytopenias compared to placebo (3.6% versus 2.0%, up to week 24). This difference was mainly driven by more leukopenias including neutropenias and reduced neutrophil counts with remibrutinib. In thrombocytopenia, the difference was 0.5% versus 0.3%.
- *Arterial hypertension*.
  In a single-arm Phase III study (A2305) with 24-hour blood pressure monitoring, treatment with remibrutinib 25 mg BID for CSU showed no clinically relevant effect on blood pressure at week 4 (steady state) (see “Pharmacodynamics”). In clinical trials with remibrutinib in CSU, slightly more patients treated with remibrutinib than with placebo (up to week 24: 1.5% versus 0.7%, and up to week 52 an additional 7 versus 1 patients) had mild to moderate transient blood pressure elevations.
- *Cardiac arrhythmias (such as atrial fibrillation or ventricular tachyarrhythmias) and heart failure*.

Remibrutinib is a human Ether-à-go-go-Related Gene (hERG) inhibitor. Based on the 192-fold safety margin, QTc prolongation is considered unlikely to occur at pharmacological exposure. In clinical trials with remibrutinib in CSU, no cardiac arrhythmias or heart failure were reported, nor did ECG evaluations or a QTc study reveal significant safety concerns (e.g. regarding QTc prolongation).

- *Malignant diseases, especially second malignancies, including non-melanoma skin cancer, but also melanoma and solid tumours*.
  In clinical trials with remibrutinib in CSU, isolated cases of various malignant and benign neoplasms occurred in patients treated with remibrutinib. A causal link cannot be proven.
- *Hepatotoxicity, including drug-induced liver injury (DILI).*
  No cases of drug-induced liver injury (DILI) were reported in the clinical trials with remibrutinib in CSU. Newly occurring alanine transaminase (ALT) elevations >5 x ULN were rare overall, but occurred in slightly more patients receiving remibrutinib than placebo (n=2 versus 0, 0.3% versus 0%). Remibrutinib binds covalently to proteins in the liver and therefore represents a theoretical risk of DILI.

Reporting suspected adverse effects after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse effects via the online portal EIViS (Electronic Vigilance System). You can find further information at www.swissmedic.ch.

Overdose

There was no experience with overdose in the pivotal phase III clinical studies with Rhapsido. Dosages 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 are to be instituted as required.

Properties/Actions

ATC code

L04AA60
Pharmacotherapeutic group: Bruton’s tyrosine kinase inhibitors.

Mechanism of action

Bruton's tyrosine kinase (BTK) is an intracellular protein selectively expressed in mast cells, basophils, B cells, macrophages and thrombocytes. BTK plays a key role in the intracellular signalling 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 that forms a covalent bond with a cysteine residue in the BTK active site, leading to durable inactivation of BTK. 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.

Pharmacodynamics

Inhibition of mast cells and basophils by remibrutinib results in reduced secretion of mast cell mediators such as histamine as well as a reduction of blood basophil surface markers CD63 and CD203c which are involved in degranulation. In addition, remibrutinib inhibits activation of autoreactive B cells via BCR and reduces antigen presentation markers such as CD69 and CD86. Based on clinical pharmacokinetic and pharmacodynamic (PK/PD) data, BTK occupancy is estimated to be ≥96% in blood, maintained throughout the entire day with remibrutinib 25 mg twice daily. An exploratory translational PK/PD model showed that 25 mg remibrutinib twice daily is estimated to achieve a trough BTK occupancy ≥80% in peripheral target tissues.

Immunoglobulins

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 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 throughout the 52 weeks in both arms.

Cardiac electrophysiology

The effects of remibrutinib on QTc interval prolongation were predicted using concentration-QTc analysis. The upper limit of the 90% confidence interval for the predicted mean change in the QTcF interval was below 10 msec at the expected C_{max} at supratherapeutic exposures. Therefore, no clinically significant prolongation of the 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 (ABPM) at steady state (week 4) compared to baseline in a multicentre, open-label, phase III study (A2305). The phase III

study enrolled 144 patients with CSU inadequately controlled by a second-generation H1 antihistamine, who received 25 mg remibrutinib BID. 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. In the interpretation, the study design (lack of a control group, number of exposed patients (N=143), and relatively short observation period (up to week 4) should be taken into account in view of the relatively long mean disease and anticipated treatment duration for CSU.

Clinical efficacy

The efficacy and safety of Rhapsido were evaluated in two identical, multicentre, randomised, 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 randomised in a 2:1 ratio to receive either 25 mg Rhapsido or placebo twice daily via the oral route for 24 weeks during the double-blind treatment period. This was followed by a 28-week, open-label treatment period, during which all patients received 25 mg Rhapsido twice daily.
REMIX-1 (NCT05030311) and REMIX-2 (NCT05032157) enrolled a total of 925 adult patients with CSU that was inadequately controlled despite treatment with second-generation H1 antihistamines (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 (number of wheals) (HSS7) ≥6 (range 0 to 21) for 7 days prior to randomisation.
The UAS7 weekly score is the sum of the HSS7 and ISS7 weekly scores (see below). It has a range of 0-42, with higher values indicating higher disease activity. According to Stull et al. 2017, the following 5 UAS7 weekly score categories are distinguished: 0 (Urticaria-free); 1-6 (Well-controlled urticaria activity), 7-15 (Mild urticaria activity), 16-27 (Moderate urticaria activity), and 28-42 (Severe urticaria activity).
The HSS7 weekly score was determined by recording the severity of wheals twice daily in an electronic diary and finally adding up the average daily values over 7 days. It has a range of 0 to 21, with higher values indicating a higher number of wheals. The following four HSS7 weekly score categories have been defined: 0 (no wheals), 1 (1-6 wheals/12 hours), 2 (7-12 wheals/12 hours), 3 (>12 wheals/12 hours).
The ISS7 weekly score was determined by recording the severity of itching twice daily in an electronic diary and finally adding up the average daily values over 7 days. It has a range of 0 to 21, with higher values indicating more severe itching. The following four ISS7 weekly score categories have been

defined: 0 (itch-free), 1 (mild itching, minimally perceived, easily tolerated), 2 (moderate itching, definitely perceived, bothersome but tolerable), 3 (severe itching, difficult to tolerate).

Demographics and baseline characteristics were generally well balanced across all groups (see Table 2). In REMIX-1 and REMIX-2, 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 in REMIX-1 and REMIX-2, respectively, had previous experience of angioedema. 68.1% and 69.2% of patients in REMIX-1 and REMIX-2, respectively, were anti-IgE biologic naive.

The mean duration of CSU at enrolment 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.

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

Parameters	**REMIX-1**			**REMIX-2**		
	Rhapsido (N=313)	**Placebo (N=157)**	**Overall (N=470)**	**Rhapsido (N=300)**	**Placebo (N=155)**	**Overall (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)
Gender n (%)						
Female n (%)	212 (67.7)	109 (69.4)	321 (68.3)	197 (65.7)	100 (64.5)	297 (65.3)
Ethnicity n (%)						
White	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)
Hispanic/Latin American	76 (24.3)	44 (28.0)	120 (25.5)	16 (5.3)	5 (3.2)	21 (4.6)
Non-Hispanic/Latin American	237 (75.7)	113 (72.0)	350 (74.5)	284 (94.7)	149 (96.1)	433 (95.2)
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)
High 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)

Parameters	REMIX-1			REMIX-2		
	Rhapsido (N=313)	Placebo (N=157)	Overall (N=470)	Rhapsido (N=300)	Placebo (N=155)	Overall (N=455)
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: 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 with well-controlled disease (UAS7 ≤6) at weeks 2 and 12
- proportion of patients with complete absence of itch and hives (UAS7 = 0) at week 12
- proportion of patients with Dermatology Life Quality Index (DLQI) score of 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 a statistically significant improvement in itch and hives symptoms in patients treated with remibrutinib compared to patients who received placebo. Results are presented in Table 3.

Table 3 Efficacy results in REMIX-1 and REMIX-2 at week 12[a, b]

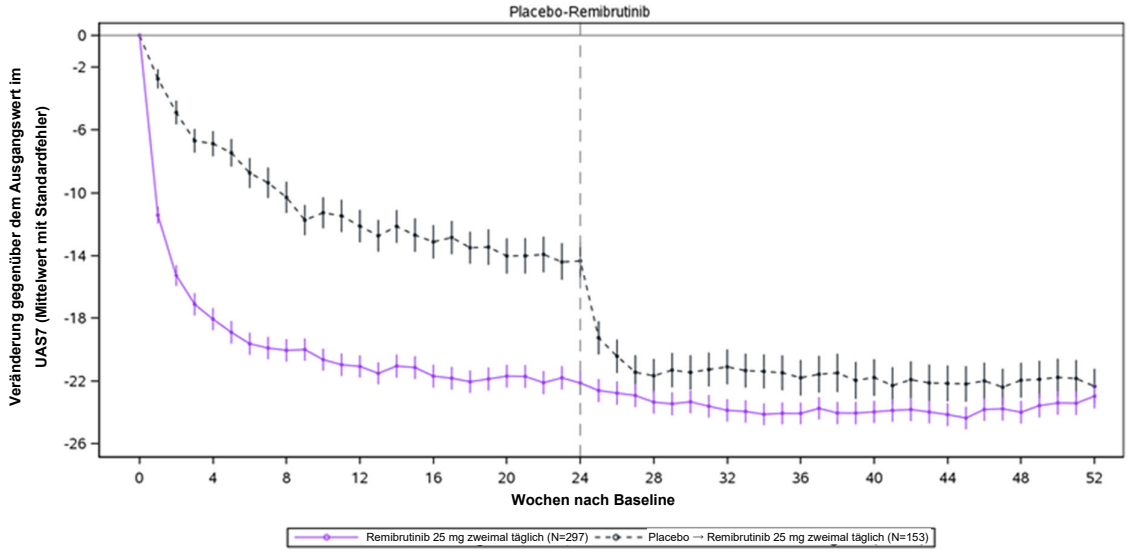
	REMIX-1		REMIX-2	
	Rhapsido (N=309)[c]	Placebo (N=153)[c]	Rhapsido (N=297)[c]	Placebo (N=153)[c]
Change from baseline in UAS7 at week 12				
LS mean (SE) CFB	–20.02 (0.716)	–13.79 (0.980)	–19.41 (0.702)	–11.73 (0.948)
Difference in LS mean (SE) vs placebo	–6.22 (1.136)		–7.68 (1.136)	
95% CI for difference	–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)	

	REMIX-1		REMIX-2	
	Rhapsido (N=309)[c]	Placebo (N=153)[c]	Rhapsido (N=297)[c]	Placebo (N=153)[c]
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)
Difference between treatment groups	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)
Difference between treatment groups	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)
Difference between treatment groups	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)
Difference between treatment groups	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 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: 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 relate to week 12)
[c] Multiple imputation techniques were implemented for missing data.

Table 3 shows statistically significant and clinically meaningful improvements in mean change from baseline in UAS7 score 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]

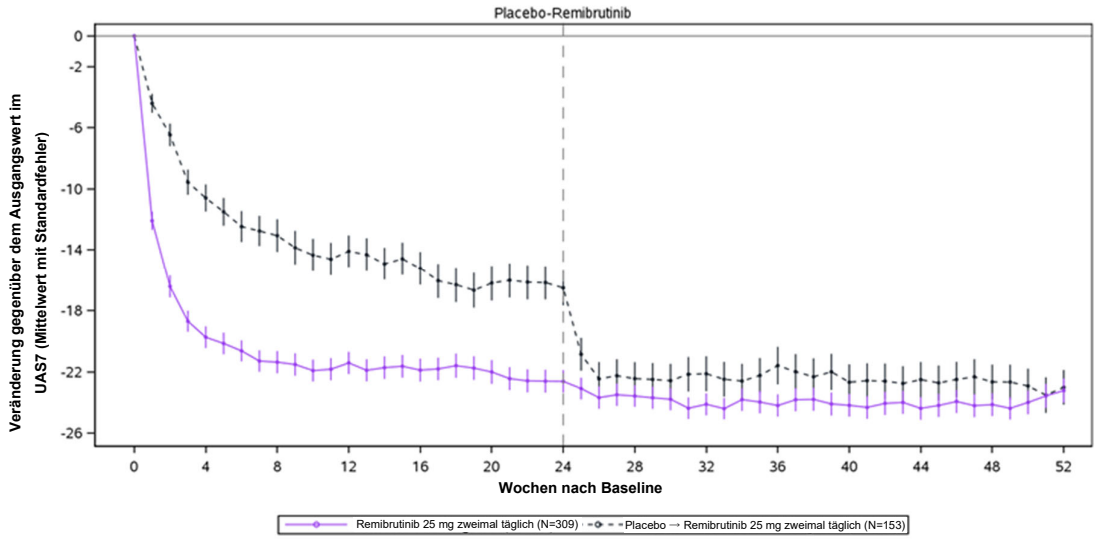


[a] In REMIX-2 at baseline, 297 patients were included in the remibrutinib arm and 153 in the placebo arm.

[b] Placebo patients were switched over to receive open-label remibrutinib treatment from week 24.

Table 3 shows statistically significant and clinically meaningful improvements in mean change from baseline in UAS7 score in REMIX-1 at week 12 in patients treated with Rhapsido versus 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 the placebo arm.

[b] Placebo patients were 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 CSU duration, previous history of angioedema, CU index, prior exposure to anti-IgE biologics and total IgE level).

Pharmacokinetics

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). The absolute oral bioavailability is 33.8% (50 mg once daily). At 25 mg twice daily, accumulation is negligible.

Food effect

Remibrutinib AUC increased by 33% and C_{max} decreased by 5%, respectively, compared to the fasted state following administration of remibrutinib (25 mg twice daily) with a high-fat meal.

Distribution

Remibrutinib is rapidly 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 analyses, the volume of distribution at steady state was 58 litres (central compartment) and 1,180 litres (peripheral compartment).

Metabolism

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

Elimination

The mean effective elimination half-life of remibrutinib was between 1 and 2 hours at steady state. Following intravenous administration of 100 mg [^{14}C]-remibrutinib, excretion of radioactivity (remibrutinib and metabolites) was approximately 70% of the administered dose in faeces and 30% in urine. Renal excretion of unchanged remibrutinib after oral administration was below 1% of the dose.

Linearity/non-linearity

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

Pharmacokinetics in special populations

A population PK (pop-PK) analysis was conducted on remibrutinib data from 1,152 patients. The analysis showed that age (18 to 80 years), sex (63.5% females and 36.5% males), ethnicity (59.3% non-Asian, 8.8% mainland Chinese, 12.2% Japanese and 19.7% other Asian) and body weight (39 to 162 kg) had no clinically relevant effect on the pharmacokinetics (PK) of remibrutinib.

Patients with 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 clearance in patients with mild (n=222), moderate (n=25) and severe renal impairment (n=1) compared to normal renal function (n=904).

Patients with hepatic impairment

The C_{max} and AUC of remibrutinib at steady state increased 1.85-fold and 2.15-fold in patients with mild hepatic impairment (Child-Pugh class A; n=8), 1.65-fold and 2.07-fold in patients with moderate hepatic impairment (Child-Pugh class B; n=7) and 1.99-fold and 3.12-fold in patients with severe hepatic impairment (Child-Pugh class C; n=7), respectively, compared to patients with normal hepatic function (n=15) following an oral dose of 25 mg remibrutinib twice daily. There was no change in protein binding of remibrutinib in patients with hepatic impairment compared to patients with normal hepatic function (see “Dosage/Administration”).

Preclinical data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology concerning respiratory or central nervous system function, repeated-dose toxicity, genotoxicity, carcinogenicity, fertility and phototoxicity. However, preclinical safety data demonstrated

effects on immune cells (inhibition of primary antibody responses) and haemostasis (inhibition of specific platelet functions).

Safety pharmacology and repeated-dose toxicity

An *in vitro* assessment of cardiovascular safety pharmacology showed inhibition of hERG with an IC_{50} of 1.4 µM (this concentration is 192 times higher than the C_{max} of the unbound substance in plasma at an MRHD of 25 mg twice daily). Furthermore, remibrutinib induced small prolongations in QTc interval at high exposure (C_{max}-based exposure 24-fold [total blood] or 46-fold [unbound plasma] compared to the MRHD of 25 mg twice daily) in a non-GLP cardiovascular study in dogs but not in any pivotal dog study.

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

Carcinogenicity and genotoxicity

Remibrutinib did not show evidence of carcinogenic potential in mouse and rat carcinogenicity studies at oral doses up to 1500 mg/kg/day (approximately 58-fold (males) and 144-fold (females) of the MRHD of 25 mg twice daily based on AUC) and 300 mg/kg/day (approximately 8-fold (males) and 98-fold (females) of the MRHD of 25 mg twice daily based on AUC), respectively.

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

Reproductive toxicity

In embryo-foetal development (EFD) studies in pregnant animals, remibrutinib was administered orally to rats at doses up to 1,000 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-foetal NOAELs were 1,000 mg/kg/day and 100 mg/kg/day, respectively, which are equivalent to 126 and 23 times the MRHD of 25 mg twice daily (based on AUC). Increased foetal external malformations (e.g. open/opaque eyes, small jaws, hyperflexion of forelimbs) and maternal toxicity (temporarily reduced food consumption and adverse clinical signs) occurred in rabbits at 300 mg/kg/day (141 times the MRHD based on AUC). It is unlikely that the foetal findings can be attributed to maternal toxicity. The dose of 450 mg/kg/day was not tolerated by pregnant rabbits.

In the pre- and postnatal development (PPND) study, remibrutinib was administered orally to pregnant rats at doses up to 1,000 mg/kg/day from gestation day 6 to lactation day (LD) 21. Remibrutinib induced adverse effects at 1,000 mg/kg/day that affected both 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 dosages up to 1,000 mg/kg/day were noted in the surviving offspring developing into adulthood. NOAEL for pregnant animals and offspring was established based on AUC at 300 mg/kg/day, which is equivalent to 67 times the MRHD of 25 mg twice daily.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage

Do not store above 30°C.
Keep out of the reach of children.
Store in the original container.

Authorisation number

70227 (Swissmedic)

Pack sizes

25 mg Rhapsido: Packs of 60 film-coated tablets [B]

Marketing authorisation holder

Novartis Pharma Schweiz AG, Risch, Switzerland; domicile: 6343 Rotkreuz, Switzerland

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