NOVARTIS

Regulatory Affairs

Remibrutinib

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name)	Remibrutinib
Product(s) concerned (brand name(s))	Rhapsido®
Document status	Final
Version number of the RMP Public Summary	1.0
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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Rhapsido is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the Arzneimittelinformation/Information sur le médicament approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Rhapsido in Switzerland is the Arzneimittelinformation/Information sur le médicament (see www.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Rhapsido.

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This is a summary of the risk management plan (RMP) for Rhapsido. The RMP details important risks of Rhapsido, how these risks can be minimized, and how more information will be obtained about Rhapsido's risks and uncertainties (missing information).

Rhapsido's prescribing information (PI) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Rhapsido should be used.

This summary of the RMP for Rhapsido should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the Swiss Public Assessment Report (Swiss PAR).

Important new concerns or changes to the current ones will be included in updates of Rhapsido's RMP.

I. The medicine and what it is used for

Rhapsido is authorised for treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1-antihistamine. It contains remibrutinib as the active substance and it is given by oral route, twice daily, Film-coated tablet, 25 mg.

Further information about the evaluation of Rhapsido benefits can be found in Rhapsido’s Swiss PAR, including in its plain-language summary, available on the Swissmedic website.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Rhapsido, together with measures to minimize such risks and the proposed studies for learning more about Rhapsido's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and PI addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status – the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Rhapsido is not yet available, it is listed under 'missing information' below.

II.A: List of important risks and missing information

Important risks of Rhapsido are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Rhapsido. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 1 List of important risks and missing information

Important identified risks	None
Important potential risks	Serious bleeding events Teratogenicity
Missing information	Safety with long term use

II B: Summary of important risks

Table 2 Important potential risk: Serious bleeding events

Evidence for linking the risk to the medicine	In Pool 1 placebo-controlled period (24 weeks), two SAEs of Bleeding AESIs occurred in the remibrutinib group (EAIR 0.8): 1) contusion related to a fall and 2) hematuria in a patient with bladder dysplasia and bladder surgery; both events were considered not related to remibrutinib. Causality with remibrutinib is confounded in both cases. No SAEs of Bleeding AESIs occurred in the placebo group. Due to small number of cases, comparison between treatment groups is limited. During the entire study period (52 weeks), in Pool 1, no additional patient experienced a serious bleeding event in remibrutinib group (EAIR 0.4) or in patients transitioning from placebo to remibrutinib, In Pool 2 (n=1234), which includes Phase II and Phase III studies,

	in Phase II extension study A2201E1 (52 weeks), one SAE (melaena) due to bariatric surgery was reported in the remibrutinib group and was considered not related to remibrutinib. Overall, the EAIR of serious bleeding events was 0.3%. In vitro assessments in human whole blood revealed an increased ROTEM EXTEM® but not FIBTEM® lysis index, as well as an inhibition of collagen-induced platelet aggregation, suggesting an impact of remibrutinib on platelets. The potential mechanism to affect platelet function based on pre-clinical evidence of bleeding justifies the classification of serious bleeding as an important potential risk.
Risk factors and risk groups	History of significant gastrointestinal bleeding or coagulation disorders, surgery, concomitant anti-coagulant treatment or anti-platelet medication are known risk factors for serious bleeding.
Risk minimization measures	Routine risk minimization measures: PI Section Dosage/Administration PI Section Interactions PI Section Adverse effects PI Section Preclinical data Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study CLOU064A2303B Study CLOU064F12301 See section II.C of this summary for an overview of the post-authorization development plan.

Table 3 Important potential risk: Teratogenicity

Evidence for linking the risk to the medicine	Teratogenicity is considered as a potential risk, based on findings in rabbits at a remibrutinib dose of 300 mg/kg/day. No effects on rat fertility and early embryonic development, or rat or rabbit embryo-fetal

	development, were seen at oral doses of remibrutinib up to 1,000 mg/kg/day (rats) or 100 mg/kg/day (rabbits). Adverse findings in a pre- and postnatal development study in rats affecting maternal animals and offspring (up to lactation day 1) were observed at the highest tested dose of 1,000 mg/kg/day. A NOAEL in rabbits was established at 100 mg/kg/day, corresponding to steady-state safety margin of 23-fold (AUC0-24h) or 36-fold (Cmax) vs clinical 25 mg b.i.d. remibrutinib in humans.
Risk factors and risk groups	Women of child-bearing potential not using effective contraception, breast feeding women.
Risk minimization measures	Routine risk minimization measures: PI Section Pregnancy/Breast-feeding PI Section Preclinical data PL Additional risk minimization measures: None

Table 4 Important Missing information: Safety with long term use

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study CLOU064A2303B Study CLOU064F12301 See section II.C of this summary for an overview of the post-authorization development plan.

II C: Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Rhapsido.

II.C.2. Other studies in post-authorization development plan

Table 5 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
Study CLOU064A2303B	The purpose of this extension study is to collect long-term efficacy, safety and tolerability data on remibrutinib 25 mg b.i.d. in a selected group of participants with CSU who previously completed the treatment phase of remibrutinib preceding Phase III studies. This study is intended to fulfill the Novartis commitment to provide post-trial access to participants who have completed the preceding Phase III studies, where applicable. Primary objective: To assess the efficacy of remibrutinib (25 mg b.i.d.) in CSU participants with a UAS7 (Weekly Urticaria Activity Score) <16 at Week 52 in the prior core study with respect to time to first of the three events: relapse or study treatment discontinuation due to lack of efficacy or intake of strongly confounding prohibited medication up to Week 24 compared to placebo. Secondary objective: To assess the long-term safety and tolerability of remibrutinib 25 mg b.i.d.
Study CLOU064F12301	The purpose of this study (i.e., core period) is to assess the efficacy, pharmacokinetics, and safety of remibrutinib 25 mg b.i.d. vs. placebo in adolescents from 12 to < 18 years of age suffering from CSU inadequately controlled by H1-AH. The purpose of the open-label extension (OLE) period is to collect long-term efficacy, safety and tolerability data on remibrutinib 25 mg b.i.d. in adolescents after having completed the core period (i.e., 24 weeks of treatment). The duration of the OLE period is approximately 3 years. This extension period will also fulfill the Novartis commitment to provide post-trial access to participants of the previous core period. As patients will be treated for longer time period in this

	part of the study (OLE), as compared to the core period, the design will allow for longer time safety monitoring. No major differences are anticipated to be seen between adult and adolescent CSU population and hence the data from this study is expected to inform long-term safety of remibrutinib. The purpose of the Long-Term Treatment-Free Follow-Up (LTTFFU) period is to collect safety data in this population for up to three years after the last dose of treatment in one of the study periods.