CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	218436
PDUFA Goal Date	September 30, 2025
Nexus TTT #	2025-13041
Reviewer Name	Lindsey W. Crist, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
Acting Division Director	Laura Zendel, PharmD
Review Completion Date	September 15, 2025
Subject	Evaluation of Need for a REMS
Established Name	Remibrutinib
Trade Name	Rhapsido
Name of Applicant	Novartis Pharmaceutical Corporation
Therapeutic Class	Kinase inhibitor
Dosage Form	Film-coated oral tablet, 25 mg
Dosing Regimen	25 mg by mouth twice daily

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Rhapsido (remibrutinib) is necessary to ensure the benefits outweigh its risks. Novartis Pharmaceuticals Corporation submitted a New Drug Application (NDA) 218436 for remibrutinib with the proposed indication for the treatment of chronic spontaneous urticaria in adult patients who remain symptomatic despite H1 antihistamine treatment. This application is under review in the Division of Pulmonology, Allergy, and Critical Care. The Applicant did not submit a REMS or risk management plan with this application.

DRM has determined that a REMS is not needed to ensure the benefits of remibrutinib outweigh its risks. The benefits of remibrutinib for the treatment of chronic spontaneous urticaria in adult patients who remain symptomatic despite H1 antihistamine treatment were demonstrated in two randomized, double-blind, placebo-controlled, phase 3, pivotal trials. Both pivotal trials demonstrated statistically and clinically significant improvements in the co-primary endpoints of weekly itch severity score and weekly hives severity score relative to placebo at week 12. The safety profile is favorable; there were no serious adverse events associated with remibrutinib that required REMS consideration. Labeling is sufficient for communicating the potential serious adverse events. Based on the available safety and efficacy data, risk mitigation beyond labeling is not required.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Rhapsido (remibrutinib) is necessary to ensure the benefits outweigh its risks. Novartis Pharmaceuticals Corporation (hereafter referred to as the Applicant) submitted a New Drug Application (NDA) 218436 for remibrutinib with the proposed indication for the treatment of chronic spontaneous urticaria in adult patients who remain symptomatic despite H1 antihistamine treatment.[1] This application is under review in the Division of Pulmonology, Allergy, and Critical Care (DPACC). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Rhapsido (remibrutinib), a NME[a], is a Bruton's tyrosine kinase inhibitor proposed for the treatment of chronic spontaneous urticaria in adult patients who remain symptomatic despite H1 antihistamine treatment.[1]

Bruton's tyrosine kinase (BTK) is an intracellular protein expressed in selected cells of the adaptive and innate immune system (e.g., mast cells, basophils, B cells, macrophages, and thrombocytes).[2,3]

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

BTK is involved in intracellular signaling pathways through the Fc epsilon receptor-1 (FcεR1), Fc gamma receptor (FcγR), and the B cell antigen receptor.[3,4] Activation initiates signaling cascades resulting in pro-inflammatory immune responses that are thought to cause the symptoms of chronic spontaneous urticaria (e.g., itch, hives, and angioedema).[4] Remibrutinib is a selective, covalent inhibitor of BTK.[4] Remibrutinib inhibits mast cell and basophil activation/degranulation and prevents the release of histamine and other pro-inflammatory mediators involved in the pathology of chronic spontaneous urticaria.

Remibrutinib is proposed to be supplied as a 25 mg film-coated oral tablet. The proposed dose of remibrutinib is 25 mg by mouth twice daily with or without food. Remibrutinib will likely be prescribed as a chronic therapy for relief of symptoms until remission occurs.[b] Remibrutinib is likely to be administered primarily in the outpatient setting by the patient or a caregiver. Remibrutinib is not currently approved in any jurisdiction.

If approved, remibrutinib would be the first BTK inhibitor for the treatment of chronic spontaneous urticaria. At the time of this review, there are several oral BTK inhibitors available in the United States that are approved for various hematology and oncology indications.[c] None of the currently approved BTK inhibitors were approved with a Boxed Warning or REMS.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 218436 relevant to this review:

- **01/31/2025**: NDA 218436 submission for the treatment of chronic spontaneous urticaria in adult patients who remain symptomatic despite H1 antihistamine treatment received. The Applicant submitted a Priority Review Voucher with this application.[1]

- **05/19/2025**: A mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for remibrutinib.

- **07/29/2025**: A late cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that no issues related to risk management have been identified to date.

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] The available BTK inhibitors include Imbruvica (ibrutinib), NDA 205552 approved in 2013; Calquence (acalabrutinib), NDA 210259 approved in 2017; Brukinsa (zanubrutinib), NDA 213217 approved in 2019; Jaypirca (pirtobrutinib), NDA 216059 approved in 2023; and rilzabrutinib, NDA 219685 approved in 2025.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Chronic spontaneous urticaria[d] (CSU), is a skin condition characterized by the spontaneous appearance of wheals (also known as hives), angioedema, or both occurring for a period of 6 weeks or longer.[5,6] CSU is distinct from urticaria and/or angioedema caused by another condition (e.g., urticarial vasculitis, autoinflammatory disease, hereditary angioedema) or trigger (e.g., external stimuli, medications).[5-7] The pathophysiology for CSU is not fully understood; however, it is thought that skin mast cell and basophil activation leads to the release of histamine and other pro-inflammatory and vasoactive mediators which cause the characteristic itchy wheals, swelling, and redness.[6,7]

Approximately 1% of the global population is affected by CSU.[6,e] The incidence ranges from 0.10-2.43 per 1000 person years.[6] CSU may occur at any age, but the typical age at onset is between 30 to 50 years.[5,6] In adults, females are affected twice as often as men.[8] The clinical presentation is characterized by the appearance of itchy wheals with surrounding erythema that may develop anywhere on a patient's body.[5,6,8] Individual wheals appear, enlarge, may merge with others, and then resolve within 24 hours without any scarring or bruising on the skin.[8] New wheals appear in the same location or other locations on the body causing persistent symptoms. Angioedema occurs in about 30 to 50% of adults with CSU.[6] Angioedema is characterized by a sudden, pronounced erythematous deep swelling in the lower dermis and subcutaneous tissues and typically affects the face, extremities, or the torso. Angioedema has a slower resolution than wheals and may take up to 72 hours to resolve.[5,8]

In moderate to severe CSU, wheals and/or angioedema may occur daily or near daily.[6] In the majority of patients CSU is an episodic and self-limited condition. The average duration of disease is two to five years.[8] The rate of spontaneous remission at one year is around 30 to 50%.[8] However, symptoms persist beyond five years in up to 30% of patients and many patients require long-term treatment to achieve relief of symptoms. Recurrent episodes may occur months or years later.[7] CSU has a significant impact on patients' quality of life as symptoms may be unpredictable and uncomfortable, impact mood and mental health, impact sleep, interfere with the ability to perform activities of daily living, and interfere with work productivity.[5,7,8,f] Patients with CSU also have a higher prevalence of psychiatric conditions, including depression and anxiety.[9]

[d] Previously referred to as chronic idiopathic urticaria

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

3.2. Description of Current Treatment Options

The goal of treatment for CSU is to resolve or reduce the signs and symptoms of active disease to provide relief until remission occurs. Treatment guidelines recommend a stepwise approach to therapy.[7,10] The treatment approach includes starting medications to improve symptoms and stepping up or down based on treatment response and disease activity.[10] Treatment should be continuous (rather than as needed) until symptoms are controlled and spontaneous remission occurs. For patients with complete response to treatment, treatment should continue for a few months and then be tapered off slowly.[7]

The recommended first-line therapy for CSU is a second-generation antihistamine (e.g., cetirizine, loratadine, etc.) administered daily at doses approved in FDA-approved labeling.[7,10] Second-generation antihistamines are favored over first-generation due to improved tolerability and duration of action; however, first-generation antihistamines have also been used for this indication. If symptoms are not controlled at standard doses, studies have demonstrated that increasing the dose up to fourfold may be effective without significant risks.[7] Some experts recommend combining two second-generation antihistamines; however, the recent international treatment guidelines suggest against this option.[7,10] Approximately 40-50% of patients with CSU are inadequately controlled on antihistamine therapy alone.[5,11]

The current treatment guidelines recommend stepping up therapy to add Xolair (omalizumab) in patients who do not respond to antihistamine therapy.[7] An efficacy supplement was approved on March 21, 2014 for Xolair (omalizumab) for the treatment of CSU in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment.[12,g] Xolair (omalizumab) has a Boxed Warning for anaphylaxis and labeling includes several risks conveyed in Section 5, Warnings and Precautions including the following: malignancy, acute asthma symptoms, symptoms similar to serum sickness, and eosinophilic conditions.[12] Labeling also includes a Medication Guide to communicate risks to patients. One of the most reliable predictors of response to Xolair (omalizumab) therapy is baseline IgE level. Non-responders often have low baseline IgE levels.[13]

On April 18, 2025, an efficacy supplement for Dupixent (dupilumab) was approved for the treatment of adults and adolescents aged 12 years and older with CSU who remain symptomatic despite histamine-1 (H1) antihistamine treatment.[14] Several risks of Dupixent (dupilumab) are conveyed in labeling in Section 5, Warnings and Precautions and include hypersensitivity; conjunctivitis and keratitis, eosinophilic conditions; acute symptoms of asthma or chronic obstructive pulmonary disease or acute deteriorating disease; risk of withdrawal symptoms with abrupt discontinuation of

[g] A REMS consisting of a Medication Guide and timetable for submission of assessments was approved on July 24, 2009 for the risk of severe allergic reactions, including anaphylaxis. The REMS was released on December 22, 2011; however, the Medication Guide was retained as part of the approved labeling.

corticosteroids; psoriasis; arthralgia and psoriatic arthritis; and parasitic infections.[14] Labeling also includes a Patient Package Insert to communicate risks to patients.

Some patients do not respond to any of the FDA-approved therapy options. Off-label options such as cyclosporine or short courses of corticosteroids may be considered; however, the evidence for efficacy is not as robust and adverse event profiles may be significant.[6,7,15] There is an unmet need for safe and effective treatment options for refractory CSU.

4. Benefit Assessment

The benefit of remibrutinib for the proposed indication was demonstrated in two identical, multicenter, randomized, double-blind, parallel-group, placebo-controlled, phase 3, pivotal trials: A2301 (National Controlled Trial [NCT] 05030311) and A2302 (NCT05032157).[16] These trials, hereafter referred to as Study A2301 and Study A2302, were identical in design and evaluated remibrutinib 25 mg twice daily compared to placebo in 925 adult subjects with CSU inadequately controlled by second generation H1 antihistamines.[h] The pivotal trials consisted of a screening period of up to 4 weeks, a double-blind treatment period of 24 weeks, an open-label treatment period with remibrutinib of 28 weeks. Eligible subjects who completed the open-label treatment period could choose to roll into an extension, phase 3 study, CLOU064A2303B (NCT05513001), hereafter referred to as Study A2303B or enter a treatment-free follow-up[i] period of 4 weeks. Study A2303B is an ongoing randomized withdrawal and open-label study followed by long-term open-label treatment cycles.[16]

Subjects in the pivotal trials were randomized in a 2:1 ratio to remibrutinib (Study A2301: N=313 and Study A2302: N=300) and placebo (Study A2301: N=157 and Study A2302: N=155) for the double-blind period. Eligible subjects consisted of subjects 18 years and older with CSU for 6 months or greater prior to screening and symptoms inadequately controlled by second generation H1 antihistamines[j]. All subjects were required to have a weekly urticaria activity score (UAS7) score ≥16, a weekly itch severity score (ISS7) ≥6, and a weekly hives severity score (HSS7) ≥6 during the 7 days prior to randomization.

The co-primary endpoints for the pivotal trials were the absolute change from baseline in ISS7 and HSS7 at week 12. Key secondary endpoints included absolute change from baseline in weekly urticaria activity score (UAS7), achievement of disease activity control (UAS7 ≤ 6), complete absence of itch and hives (UAS7 = 0), early onset of disease control at Week 2, improvement in dermatology-related quality of life

[h] CSU inadequately controlled despite treatment with H1 antihistamines was defined by the presence of itch and hives for ≥ 6 consecutive weeks.

[i] All subjects who chose not to roll into the extension or any subjects who discontinued treatment prematurely entered this treatment-free period to allow assessment of safety of treatment discontinuation and to assess for potential recurrence of CSU symptoms after treatment completion.

[j] Defined as the presence of itch and hives for at least 6 consecutive weeks or greater prior to screening despite the use of a second-generation antihistamines during this period.

(DLQI = 0-1), and measures of sustained disease control and angioedema management over the 12-week primary evaluation period.

Demographics and baseline characteristics were generally well balanced across the groups in both pivotal trials. The mean duration of CSU at enrollment was 6.6 and 5.2 years in Study A2301 and Study A2302, respectively. At baseline, 63.4% of the patients in Study A2301 and 59.1% of the patients in Study A2301 had severe disease defined by UAS7 ≥28 and 35.1% and 38.7% had moderate disease defined by (UAS7 16 and <28), respectively.

The efficacy results were based on results from 912 subjects who received at least one dose of treatment during the 24-week double-blind period. A statistically significant improvement was demonstrated in the co-primary endpoints of ISS7 and HSS7 relative to placebo at week 12 (see table). Remibrutinib also demonstrated a statistically significant improvement on secondary endpoints including rates of disease activity control (UAS7 ≤ 6) and complete symptom resolution (UAS7 = 0).

Table 1. Efficacy Results in Pivotal Trials

	Study A2301		**Study A2302**	
	Remibrutinib (N=309)	Placebo (N=153)	Remibrutinib (N=297)	Placebo (N=153)
Change from baseline in ISS7 at week 12				
LS mean (SE)	-9.52 (0.34)	-6.89 (0.47)	-8.95 (0.34)	-5.72 (0.45)
Treatment Difference in LS mean	-2.63		-3.23 (0.55)	
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)	-10.47 (0.40)	-6.86 (0.55)	-10.47 (-0.39)	-6.00 (-0.53)
Treatment Difference in LS mean	-3.61		-4.47	
95% CI for difference	-4.85, -2.36		-5.71, -3.23	
p-value	<0.001		<0.001	

LS Mean: Least squares mean, SE: standard error, CI: confidence interval, p-value: one-sided p-value.

Source: Adapted from Draft Prescribing Information

The review team concluded there is substantial evidence of effectiveness to support approval based on the results from the two pivotal trials which demonstrated statistically and clinically significant improvement in the co-primary endpoints relative to placebo.[17,k]

[k] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5. Risk Assessment & Safe-Use Conditions

The primary safety population for remibrutinib consists of the pooled data from the two identical phase 3, pivotal trials Study A2301 and A2302. The primary safety population included 912 adults with CSU with 606 subjects in the remibrutinib group and 306 in placebo group.[17,18] Supportive data, especially for long term use, included the 28-week open label treatment period from the pivotal trials.[17]

The most common adverse reaction reported in ≥3% of subjects with CSU treated with remibrutinib during the 24-week double-blind treatment period included nasopharyngitis (11%), bleeding[l] (9%), headache (7%), nausea (3%), and abdominal pain (3%).[19] The severity of all adverse drug reactions was mild to moderate. No severe bleeding reactions occurred. If approved, the risk of bleeding will be conveyed in Section 5, Warnings and Precautions. During the pivotal trials, which extended up to 56 weeks including a 4-week follow-up period, the remibrutinib group achieved a median exposure duration of 52 weeks with a cumulative exposure of 672 patient-years.[17]

There were no deaths in the clinical development program.[17,18] Treatment-emergent serious adverse events (SAEs)[m] occurred in 20 (3.3%) of subjects in the remibrutinib group and 7 (2.3%) of subjects in the placebo group during the placebo-controlled periods of the pivotal trials. The most common system organ class for SAEs (defined as >0.5% in any treatment group) was infections and infestations (0.7% in both the remibrutinib and placebo groups) and musculoskeletal and connective tissue disorders (0.7% in the remibrutinib group and none in the placebo group).[18]

As a class, BTK inhibitors have been associated with several adverse events including infections, cytopenias, bleeding, cardiac adverse events (atrial fibrillation/cardiac arrhythmias), and drug-induced liver injury.[17] The potential adverse event profiles vary depending on the pharmacokinetic and pharmacodynamic profiles of each product. Less selective BTK inhibitors have more off-target adverse events. Remibrutinib is considered a selective inhibitor and has a favorable safety profile for the target population based on the available data.[17] Drug induced liver injury is discussed more below in Section 5.1.

5.1. Drug-induced Liver injury

BTK inhibitors have been associated with drug-induced liver injury. The risk varies across products within the class and may be related to differences in pharmacokinetic and pharmacodynamic properties and different mechanisms of injury. Labeling for this risk is included in Section 5, Warnings and Precautions, for the approved BTK inhibitors.

[l] Bleeding included conjunctival bleeding, contusion, ecchymosis, epistaxis, gingival bleeding, hematoma, hematuria, hemorrhagic ovarian cyst, intermenstrual bleeding, petechia, purpura, and urinary occult blood.

[m] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

There were no cases of severe drug-induced liver injury or cases that met criteria for Hy's Law in the clinical trials for remibrutinib.[17] A consult by the Division of Applied Regulatory Sciences was completed on May 2, 2025, to provide a hepatotoxicity risk assessment for several BTK inhibitors, including remibrutinib.[20] Remibrutinib is a second-generation BTK inhibitor. It has properties that appear to reduce the risk of hepatotoxicity such as high-selectivity for BTK which minimizes off-target effects, lower tissue accumulation, and non-CYP metabolism with inert metabolites.[20]

Exposure of remibrutinib is increased in patients with mild, moderate, and severe hepatic impairment (Child-Pugh Class A, B, and C) relative to patients with normal hepatic function.[17-19] The review team concluded that the liver safety profile for remibrutinib was characterized by infrequent, asymptomatic, and reversible transaminase elevations with rates comparable to placebo. There does not appear to be a significant hepatotoxicity risk for the treatment of CSU and there is not a need for intensive monitoring beyond normal clinical practice.[17] The proposed labeling will recommend avoiding remibrutinib in patients with liver impairment at baseline in Section 8.[19]

6. Expected Postmarket Use

Patients with chronic spontaneous urticaria usually present to their primary care providers (PCP) for evaluation and initial treatment of symptoms. If first-line options fail, patients may continue to be treated by a PCP or may be referred to specialists in allergy/immunology or dermatology.[5] Referral to a specialist is preferred for patients with refractory CSU.[7] Remibrutinib is proposed as a second-line therapy in patients who remain symptomatic despite H1 antihistamine treatment; therefore, the anticipated prescribers are likely to include allergists/immunologists, dermatologists, and PCPs. These prescribers should be able to monitor and manage any adverse effects associated with remibrutinib.

Remibrutinib is likely to be used in both the outpatient and inpatient settings administered orally by the patient or caregiver. It is intended as a chronic therapy to relieve CSU symptoms until disease activity is controlled and remission occurs. A patient package insert (PPI) is proposed to convey important counseling information.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for remibrutinib beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The clinical reviewer recommends approval of remibrutinib on the basis of the efficacy and safety information currently available.

CSU is characterized by recurrent episodes of urticaria and/or angioedema that has a significant impact on quality of life. First-line treatment is second-generation antihistamines; however, many patients have an inadequate response. Second-line options include adding on Xolair (omalizumab) or Dupixent (dupilumab). However, some patients do not respond to any of the FDA-approved options and off-label

options such as cyclosporine or corticosteroids have significant adverse event profiles. There is a need for additional treatment options for CSU. If approved, remibrutinib would be the first BTK inhibitor approved for CSU.

The benefits of remibrutinib for the treatment of treatment of chronic spontaneous urticaria in adult patients who remain symptomatic despite H1 antihistamine treatment were demonstrated in two randomized, double-blind, placebo-controlled, phase 3, pivotal trials. In both pivotal trials, a statistically significant improvement was demonstrated in the co-primary endpoints of ISS7 and HSS7 relative to placebo at week 12.

The safety profile is favorable; there were no serious adverse events associated with remibrutinib that required REMS consideration. Although this drug class has been associated with drug-induced liver injury, this risk is not anticipated to be a significant concern for remibrutinib as there are important pharmacokinetic and pharmacodynamic property differences that decrease the likelihood of liver injury. Labeling is sufficient to convey the risks to prescribers and patients. The review team concluded this option provides an oral treatment option with a favorable benefit-risk profile

Based on the available safety and efficacy data, this reviewer is not recommending a REMS and concludes that risk mitigation beyond labeling is not required.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for remibrutinib to ensure the benefits outweigh the risks. At the time of this review, evaluation of labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

Should DPACC have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. References

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