CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

218436Orig1s000

Trade Name:	Rhapsido tablets
Generic or Proper Name:	remibrutinib
Sponsor:	Novartis Pharmaceuticals Corporation
Approval Date:	September 30, 2025
Indication:	For the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment.

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 218436

NDA APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Leigh Strachan
Sr. Global Program Regulatory Manager, Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Leigh Strachan:

Please refer to your new drug application (NDA) received January 31, 2025, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rhapsido (remibrutinib) tablets.

This NDA provides for the use of Rhapsido (remibrutinib) tablets for the treatment of chronic spontaneous urticaria (CSU) in adult patients who remain symptomatic despite H1 antihistamine treatment.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 218436**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Rhapsido (remibrutinib) tablets shall be 24 months from the date of manufacture when stored at 20°C to 25°C.

Results of ongoing stability studies should be submitted throughout the dating period in your annual report, as they become available, including the results of stability studies from the first three production lots.

ADVISORY COMMITTEE

Your application for Rhapsido was not referred to an FDA advisory committee because evaluation of the safety data when used in the treatment of CSU did not raise significant safety or efficacy issues in the intended population and there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth to less than 6 years because it would be impossible or highly impracticable to conduct a study in patients in this age group who have failed to adequately respond to antihistamines (approved in patients 2 years and older for CSU) and based on the difficulty of definitive diagnosis of CSU in children under 6 years through stepwise evaluation and treatment.

We are deferring submission of your pediatric study for ages 6 to 11 years for this application until data are available in adolescents and evaluation of the juvenile toxicity study in rats is complete.

We are deferring submission of your pediatric studies for ages 12 to 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

4896-1 Conduct a 24-week randomized, double-blind, placebo-controlled, parallel-group study in pediatric patients aged 12 to less than 18 years with chronic spontaneous urticaria who remain symptomatic despite H1-antihistamine treatment to assess the efficacy, safety, and pharmacokinetic responses to remibrutinib.

Study Completion:	September 2027
Final Report Submission:	February 2028

4896-2 Conduct a 24-week, open-label, pharmacokinetic study in pediatric patients aged 6 to less than 12 years with chronic spontaneous urticaria who remain symptomatic despite H1-antihistamine treatment.

Final Protocol Submission:	December 2027
Study Completion:	October 2030
Final Report Submission:	March 2031

4896-3 Conduct an additional oral (gavage) juvenile toxicity study in the rat. The age of rats at study start should be equivalent to pediatric patients approximately 6 years old. The study should include ophthalmic examinations performed pre-study, at the end of the dosing period, and at the end of the recovery period. Potential neurobehavioral effects should also be evaluated in animals at the end of the dosing and recovery periods.

Draft Protocol Submission:	September 2026
Final Protocol Submission:	February 2027
Study Completion:	May 2027
Final Report Submission:	August 2027

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

[3] See the guidance for industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019) https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Submit the protocols to your IND 131325, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of adverse maternal, fetal, and infant outcomes resulting from the use of remibrutinib during pregnancy and to identify an unexpected serious risk of the potential presence of remibrutinib in human breast milk resulting in effects on the breastfed infant.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4896-4 Collect data from a prospective pregnancy exposure registry, preferably a disease-based multiproduct pregnancy registry, using a cohort analysis that compares the maternal, fetal, and infant outcomes of women exposed to remibrutinib during pregnancy with an appropriate comparator population(s). Collect data outside the U.S. to reach the target sample size, if feasible. The registry will identify and record major and minor congenital malformations, pregnancy complications, spontaneous abortion, stillbirths, neonatal deaths, pregnancy terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. These outcomes should be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you submitted on September 19, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	June 2026
Final Protocol Submission:	June 2027
Interim Reports:	June 2028
	June 2029
	June 2030
	June 2031
	June 2032
	June 2033
	June 2034
	June 2035
	June 2036
	June 2037
Study Completion:	June 2038
Final Report Submission:	December 2038

4896-5 Conduct a retrospective pregnancy cohort study using claims or electronic health record data with medical chart validation that is adequately powered to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to remibrutinib during pregnancy compared to appropriate comparator population(s).

The timetable you submitted on September 19, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	June 2026
Final Protocol Submission:	June 2027
Interim Reports:	June 2029
	June 2030
	June 2031
	June 2032
Study Completion:	June 2033
Final Report Submission:	December 2033

4896-6 Perform a milk-only lactation study in lactating women who have received remibrutinib to measure concentrations of remibrutinib in breast milk using a validated assay. Assess the effects on the breastfed infant, if available, based on study population.

The timetable you submitted on September 19, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	March 2026
Final Protocol Submission:	July 2026
Study Completion:	July 2028

Final Report Submission: September 2028

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocols to your IND 131325 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o), REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o), REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o).**

Submission of the protocols for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-*

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019). https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.[5]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website.[8]

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[8] https://www.uspnf.com/

If you have any questions, contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648 or phuong.ton@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Kathleen Donohue, MD
Deputy Director
Office of Immunology and Inflammation (OII)
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KATHLEEN M DONOHUE
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