CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

207997Orig1s000
207997Orig2s000

Trade Name:	**RYDAPT**
Generic Name:	**Midostaurin**
Sponsor:	**Novartis Pharmaceuticals Corporation**
Approval Date:	**April 28, 2017**
Indication:	**Treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).** **Treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutation-positive as detected by an FDA approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation**.

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207997Orig1s000
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APPLICATION NUMBER:

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207997Orig2s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207997 Original #1
NDA 207997 Original #2

NDA APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Abbey Abraham, PharmD
Regulatory Affairs, Therapeutic Area Director
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Abraham:

Please refer to your New Drug Application (NDA) dated August 29, 2016, received August 29, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for RYDAPT® (midostaurin) capsules, 25 mg.

This new drug application provides for the use of RYDAPT® (midostaurin) for the following indications which, for administrative purposes, we have designated as follows:

- NDA 207997/Original #1 – treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).

- NDA 207997/Original #2 – treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutation-positive as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.

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 text.

EXPIRATION DATING PERIOD

Expiration dating period of 36 months for the drug product when stored at 25°C (77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F).

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

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). 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*," available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on February 28, 2017, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry "*Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" (May 2015, Revision 3)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 207997**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for RYDAPT was not referred to an FDA advisory committee because the clinical trial design is acceptable.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for these indications has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (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 embryo-fetal toxicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

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

PMR 3210-1 Establish a worldwide Pregnancy Surveillance Program (enhanced pharmacovigilance) to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women exposed to midostaurin during pregnancy. Add notice of the Pregnancy Surveillance Program and telephone contact number (and/or website) to the prescribing information. Provide a complete protocol which includes details regarding how you plan to encourage patients and providers to report pregnancy exposures (e.g., telephone contact number and/or website in prescribing information), measures to ensure complete data capture regarding pregnancy outcomes and any adverse effects in offspring, and plans for comprehensive data analysis and yearly reporting. Submit yearly reports on the cumulative findings and analyses from the Pregnancy Surveillance Program.

The timetable you submitted on April 18, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 6/2017
Final Protocol Submission: 8/2017
Revised Prescribing Information: 12/2017
Interim Report #1: 06/2018
Interim Report #2: 06/2019
Interim Report #3: 06/2020
Interim Report #4: 06/2021
Interim Report #5: 06/2022
Interim Report #6: 06/2023
Interim Report #7: 06/2024
Interim Report #8: 06/2025
Interim Report #9: 06/2026
Study Completion: 04/2027
Final Report Submission: 06/2027

Submit clinical protocols to your IND 057120 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports 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 protocol(s) 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 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

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 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 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

PMC 3210-2 To corroborate your assertion that midostaurin induces a treatment benefit in the overall population of patients with FLT3 mutations rather than in only a subset of patients with a mutation in a different kinase inhibited by the drug, provide subgroup analyses for CR, OS and EFS by genomic mutations that occurred concurrently with FLT3 for randomized subjects who consented for additional molecular studies in the RATIFY trial. Submit a data file with results of the full mutational profiling at baseline performed by Novartis in close collaboration with Alliance and RATIFY Cooperative Groups / Investigators in addition to the full study report.

The timetable you submitted on February 24, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission	06/2017
Final Protocol Submission	12/2017

Study Completion	04/2018
Final Report Submission	10/2018

PMC 3210-3 To demonstrate that the treatment effect of midostaurin is consistent across prognostic subgroups, provide subgroup analyses for randomized subjects with cytogenetic/molecular prognostic information in the RATIFY trial for CR, OS and EFS by cytogenetic/molecular prognostic category using an accepted consensus prognostic classification, such as that published in 2016 or later by the European Leukemia Net (ELN) or the National Comprehensive Cancer Network (NCCN). Submit a data file with results of the full karyotype description at baseline performed by Alliance and/or Novartis in addition to the full study report.

The timetable you submitted on February 24, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission	06/2017
Final Protocol Submission	12/2017
Study Completion	04/2018
Final Report Submission	10/2018

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf.

Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics 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.

If you have any questions, call Kimberly Scott, Regulatory Project Manager, at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, MD
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD PAZDUR
04/28/2017