



NDA 204819/S-020

SUPPLEMENT APPROVAL

Bayer HealthCare Pharmaceuticals Inc.
Attention: Walid Kassaoui, PharmD
Senior Manager, US Regulatory Affairs
100 Bayer Boulevard
P.O. Box 0915
Whippany, NJ 07981

Dear Dr. Kassaoui:

Please refer to your supplemental new drug application (sNDA) dated and received March 9, 2026, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Adempas (riociguat) tablets.

This Changes Being Effected in 30 Dayssupplemental new drug application provides for the following proposed modifications to the approved Riociguat Shared System (SS) risk evaluation and mitigation strategy (REMS).

We have completed our review of this supplemental application. It is approved effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The Shared System (SS) REMS for Riociguat, of which Adempas is a member, was originally approved on September 1, 2022. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS consist of functionality improvements to the REMS website, updates to REMS materials to correct typographical errors, and editorial and formatting revisions..Your proposed modified REMS, submitted on March 9, 2026, amended, and appended to this letter, is approved.

This shared system REMS, known as the Riociguat Shared System REMS, currently includes products listed on the FDA REMS website.

Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS remains the same as that approved on September 1, 2022.

The revised REMS assessment plan must include, but is not limited to, the following:

Program Implementation and Operations

1. REMS Certification and Enrollment Data (provide previous, current and cumulative reporting periods):
 - a. Pharmacies
 - i. Number and percentage of newly certified pharmacies stratified by pharmacy type (inpatient and specialty)
 - (1) Number and percentage of active certified pharmacies (i.e., have dispensed riociguat) stratified by pharmacy type (i.e., inpatient and specialty) and geographic region (as defined by US Census)
 - ii. Identity of the specialty pharmacies
 - b. Healthcare Providers
 - i. Number and percentage of newly certified healthcare providers and the number and percentage of active healthcare providers (i.e., who have prescribed riociguat) stratified by medical specialty and geographic region (as defined by US Census)
 - c. Patients
 - i. Number and percentage of newly enrolled patients and the number and percentage of active patients (i.e., have received riociguat) stratified by geographic region (defined by US Census) and by patient type:
 - (1) Females of reproductive potential (FRP)
 - (2) Pre-pubertal females (as classified on the Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form) (PPF)
 - (3) Females of non-reproductive potential (FNRP)
 - d. Wholesaler/Distributors
 - i. Number and percentage of wholesaler/distributors newly authorized to distribute and the number and percentage of active wholesaler/distributors (i.e., have shipped riociguat)
 - ii. Identity of the wholesaler(s)/distributor(s)
 - iii. Number of samples provided by prescribers to patient
 - (1) Number of times more than one sample pack was provided to a patient at one time.
2. Riociguat Utilization Data (provide previous, current, and cumulative reporting periods)
 - a. Number and percentage of unique patients who received riociguat, new and total, by patient type grouped by the following age ranges:
 - i. < 10
 - ii. 10 - <18
 - iii. 18 - <25
 - iv. 25 - <45

- v. 45 - <53
 - vi. 53+
 - b. Number and percentage of outpatient prescriptions (first-fills and refill) dispensed for FRPs and FNRP stratified by:
 - i. Prescriber Specialty
 - ii. Reproductive Status (FRP or FNRP)
 - iii. Patient age as outlined in 2a above
 - c. Number and identity of the enrolled wholesaler(s)/distributor(s)
 - d. Number of sample packs provided by healthcare providers to patients
 - i. Number of times more than one sample pack was provided to a patient at one time
3. Pharmacy and Distributor Audit Summary (provide previous, current, and cumulative reporting period)
- a. Provide a report of audit findings for each stakeholder (e.g. certified specialty pharmacies; certified inpatient pharmacies, the REMS Coordinating Center, distributor and companies that distributed riociguat samples) including but not limited to:
 - i. A copy of the site-audit plan for each stakeholder
 - ii. The number of audits expected, and the number of audits conducted in each category listed directly above
 - iii. A summary of critical, major, and minor (define each category) observations identified during audits and corrective actions taken to address any non-compliance including whether any required corrective and preventive action (CAPA) plans were initiated and satisfactorily completed within one month
 - (1) For any that did not complete the CAPA within one month of the audit, describe actions taken
 - (2) Use a unique ID for each stakeholder that had deviations to track deviations by stakeholder over time
 - (3) Confirm documentation of completion of training for relevant pharmacy staff
 - (4) Verify the existence of documented processes and procedures for complying with the REMS
 - iv. A comparison of the findings to findings of previous audits and an assessment of whether any trends are observed
4. REMS Compliance (provide previous, current, and cumulative reporting period)
- a. Provide a copy of the Non-Compliance Plan which addresses the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each event, and under what circumstances a stakeholder would be suspended or de-certified from the REMS
 - b. The number of instances of noncompliance accompanied by a description of

- each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:
- i. The unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time
 - ii. The source of the noncompliance data
 - iii. The results of root cause analysis
 - iv. What action(s) were taken in response and whether any follow up is planned
- c. The number of certified pharmacies and the number of certified healthcare providers for which non-compliance with the REMS Program is detected, how such non-compliance was detected, and what action(s) were taken in response.
 - d. Number of riociguat prescriptions dispensed that were written by non-certified or deactivated prescribers, source of report(s), actions taken to prevent future occurrences, and the outcome of such actions
 - e. Number of prescriptions dispensed by non-certified pharmacies, source of report(s), actions taken to prevent future occurrences, and outcome of such actions
 - f. Number of shipments sent to non-certified pharmacies, source of report(s), actions taken to prevent future occurrences, actions taken to recover the riociguat from the non-certified pharmacy, and outcome of such actions
 - g. Number of samples sent to non-certified prescribers, actions taken to prevent future occurrences, actions taken to recover the samples from the healthcare providers, and the outcome of such actions
 - h. The number of certified healthcare providers and/or pharmacies that have had their certification suspended or revoked, including the reasons for such action
 - i. An evaluation of dispensing delays which resulted in an actual treatment interruption (defined as a delay in treatment of five or more days) focusing especially on delays on pregnancy testing with a root cause analysis to identify why pregnancy testing wasn't completed or the source of the healthcare provider and/or pharmacy error. For each treatment interruption include:
 - i. The mean and median duration (including the standard deviation) of the observed treatment interruptions
 - ii. Any adverse events resulting from the treatment interruption.
 - iii. A root cause analysis to identify why the pregnancy testing was not completed, the source of the pharmacy and/or prescriber error and the protocol used to conduct this root cause analysis
 - j. Number of prescriptions dispensed of greater than 30-day supply and a breakdown of reasons such dispensations, (i.e., prescriber authorization, prescriber non-compliance, other), include any

corrective actions as appropriate

- k. Noncompliance with the REMS requirements, source of report(s), and any corrective action(s) or resolution(s)

Safe Use Behaviors

5. Report on Change in Reproductive Potential Status Changes and Pre-pubertal Annual Verification Form Data (provide previous, current, and cumulative reporting periods)
Both in a flowchart and in the report narrative, report the following regarding the **Riociguat REMS Change in Reproductive Potential Status and Prepubertal Annual Verification Forms** including:
 - a. Number of forms received, including the number of forms received in error and the reasons these were classified as errors
 - b. Number of status changes to FRP status, including rationale for the change as indicated on the form. Also report:
 - i. Time between receipt of form and confirmation that monthly pregnancy testing occurred (time reported as a mean, median and standard deviation)
 - ii. Verification that routine monthly pregnancy tests of all FRPs occurred prior to the next dispensing of riociguat following a change in status to FRP
 - iii. Number of times riociguat was dispensed prior to the patient getting her first pregnancy test following the status change to FRP, any resulting adverse events, and corrective action
 - c. Number of status changes to a FNRP, including rationale for the change as indicated on the form
 - d. The number of Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Forms returned reporting annual verification that a patient remains a Pre-Pubertal Female
 - e. The expected number of Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Forms returned reporting annual verification that a patient remains a Pre-Pubertal Female:
 - i. For any forms expected for a Pre-Pubertal female, but not received, conduct follow-up in order to determine the cause, outcome and any corrective actions taken.
 - f. Number of shipments suspended as a result of the prescriber's failure to return the Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form for pre-pubertal females
 - g. Number of instances where a prescriber did not report a change or misclassification in the reproductive status of any female patient within 10 business days after the Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form is signed.

- h. Conduct a root cause analysis of all cases of reproductive status misclassifications and include the protocol used to conduct this root cause analysis.

Health Outcomes and/or Surrogates of Health Outcomes

- 6. Pregnancy cases (provide previous, current and cumulative reporting period)
 - a. An analysis of all cases of pregnancy reported in association with riociguat from any source with attention to but not limited to:
 - i. The number of pregnancy exposures reported and stratified by source of exposure report (i.e., spontaneous report, reported via the REMS, etc.)
 - ii. Pregnancy rate. Include incidence rates (in person years) for pregnancy cases to allow comparison with expected rates in the general population.
 - iii. A cumulative summary of both U.S. and worldwide pregnancy cases should be provided and at a minimum, include the following information:
 - (1) Event Identification Number
 - (2) Indication for riociguat
 - (3) Contraceptive methods used
 - (4) Weeks gestation at termination if pregnancy terminated
 - (5) Outcome for each pregnancy
 - (6) Age of patient
 - iv. Follow-up of outstanding pregnancy reports from the previous assessment reporting period
 - v. Root cause analysis of each reported pregnancy to determine the reason the REMS failed to prevent the pregnancy exposure. This root cause analysis should include patient interviews as a component. Include the protocol utilized to conduct this root cause analysis
 - vi.

Knowledge

- 7. Evaluation of Knowledge of the Riociguat REMS and Risks of Riociguat/Surveys (per reporting period)
 - a. An evaluation of certified healthcare provider's knowledge of:
 - i. The risks of embryo-fetal toxicity associated with riociguat
 - ii. The need for appropriate baseline and monthly monitoring
 - iii. The need to counsel patients about these risks; the need to use reliable contraception and the need for appropriate monitoring; and
 - iv. The need to enroll patients in the Riociguat REMS
 - b. An evaluation of certified inpatient and outpatient pharmacy authorized representatives' and trained pharmacists' knowledge of:

- i. The risks of embryo-fetal toxicity associated with riociguat; and
- ii. The need to confirm that appropriate patient monitoring and counseling occur before dispensing riociguat.
- c. An evaluation of patients' knowledge of:
 - i. The risks of embryo-fetal toxicity associated with riociguat
 - ii. The need for appropriate baseline and monthly monitoring; and
 - iii. Reliable contraception.

8. Overall Assessment of REMS

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support*

the modification, including: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications,* provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 204819 REMS ASSESSMENT METHODOLOGY PROTOCOL REVIEW
(insert concise description of content in bold capital letters, e.g.,
SURVEY METHODOLOGIES, AUDIT PLAN, NONCOMPLIANCE PLAN, DRUG USE STUDY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 204819 REMS ASSESSMENT

or

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

**NEW SUPPLEMENT FOR NDA 204819/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 204819/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 204819/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING
CHANGES SUBMITTED IN SUPPLEMENT XXX**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 204819/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 204819

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word and PDF format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word and PDF format are preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling*. For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

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

If you have any questions, contact Lori Anne Wachter, RN, BSN, RAC, Regulatory Project Manager for Safety, at 301 796-3975 or lori.wachter@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Selena DeConti, PharmD, MPH
Deputy Director for Safety
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology
and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- REMS

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/

SELENA D DECONTI
05/08/2026 08:22:39 AM