

# Risk Evaluation and Mitigation Strategy (REMS) Document

## Adempas (riociguat) REMS Program

### I. Administrative Information

Application Number: NDA 204819

Application Holder: Bayer HealthCare Pharmaceuticals, Inc.

Initial REMS Approval: 10/2013

Most Recent REMS Update: 02/2020

### II. REMS Goal

The goal of the Adempas REMS Program is to mitigate the risk of embryo-fetal toxicity associated with Adempas by:

1. Ensuring prescribers are educated on the following:
  - the risk of embryo-fetal toxicity
2. Ensuring prescribers are educated on and adhere to the following:
  - counseling patients about the risk and the need for monthly monitoring
  - enrolling patients in the Adempas REMS Program
  - monitoring patients at baseline and monthly
3. Ensuring that pharmacies are educated on the following:
  - the risk of embryo-fetal toxicity
4. Ensuring that pharmacies are educated on and adhere to the following:
  - confirming that the appropriate patient monitoring and counseling has occurred before dispensing Adempas
5. Ensuring that patients are informed about:
  - the risk of embryo-fetal toxicity
  - appropriate baseline and monthly patient monitoring
  - appropriate contraception

### III. REMS Requirements

**Bayer HealthCare Pharmaceuticals, Inc. must ensure that healthcare providers, patients, pharmacies, and wholesalers-distributors comply with the following requirements:**

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#### 1. Healthcare Providers who prescribe Adempas must:

To become certified to prescribe

1. Review the drug's Prescribing Information.
  2. Review the following: [Prescriber and Pharmacy Guide](#).
  3. Enroll in the REMS by completing the [Prescriber Enrollment and Agreement Form](#) and submitting it to the REMS Program.
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Before treatment initiation (first dose)	<ol style="list-style-type: none"> <li>4. For all females: Assess the patient's reproductive status using the definitions in the <a href="#">Prescriber and Pharmacy Guide</a>. Document and submit the results to the REMS Program using the <a href="#">Patient Enrollment and Consent Form</a>.</li> <li>5. For all females: Counsel the patient that the drug is only available through a restricted distribution program.</li> <li>6. For females of reproductive potential: Counsel the patient on the risk of embryo-fetal toxicity, the need to use effective contraception during treatment and for one month following treatment discontinuation, emergency contraception, and to immediately contact her prescriber if she misses a menstrual period or suspects that she is pregnant using the <a href="#">Guide for Female Patients</a>.</li> <li>7. For females of reproductive potential: Assess the patient's pregnancy status by ordering and reviewing her pregnancy test result.</li> <li>8. For pre-pubertal females: Counsel the patient on the risk of embryo-fetal toxicity and to immediately contact her prescriber if she begins to menstruate - using the <a href="#">Guide for Female Patients</a>.</li> <li>9. Enroll all female patients by completing and submitting the <a href="#">Patient Enrollment and Consent Form</a> and submitting it to the REMS Program.</li> </ol>
During treatment; before each prescription	<ol style="list-style-type: none"> <li>10. For females of reproductive potential: Counsel the patient if she is not complying with the required testing or if she is not using effective contraception, and to immediately contact her prescriber if she misses a menstrual period or suspects that she is pregnant.</li> <li>11. For females of reproductive potential: Assess the patient's pregnancy status by ordering and reviewing her pregnancy test result.</li> </ol>
During treatment; at least annually	<ol style="list-style-type: none"> <li>12. For pre-pubertal females at least age 8 years or older: Document reproductive status and submit to the REMS Program using the <a href="#">Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form</a>.</li> </ol>
After treatment discontinuation; one month	<ol style="list-style-type: none"> <li>13. For females of reproductive potential: Assess the patient's pregnancy status by ordering and reviewing her pregnancy test result.</li> </ol>
At all times	<ol style="list-style-type: none"> <li>14. For pre-pubertal females: Assess the patient's reproductive status.</li> <li>15. Report pregnancies to Bayer HealthCare Pharmaceuticals, Inc.</li> </ol>
At all times; within 10 business days	<ol style="list-style-type: none"> <li>16. Report a change or misclassification in reproductive status to the REMS Program using the <a href="#">Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form</a>.</li> </ol>

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## 2. Females of reproductive potential who are prescribed Adempas:

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Before treatment initiation	<ol style="list-style-type: none"><li>1. Review the <a href="#">Guide for Female Patients</a>.</li><li>2. Get a pregnancy test.</li><li>3. Enroll in the REMS Program by completing the <a href="#">Patient Enrollment and Consent Form</a> with the prescriber. Enrollment information will be provided to the REMS Program.</li><li>4. Receive counseling from the prescriber on the risk of embryo-fetal toxicity, the need to use effective contraception during treatment and for one month following treatment discontinuation, emergency contraception, and to immediately contact her prescriber if she misses a menstrual period or suspects that she is pregnant using the <a href="#">Guide for Female Patients</a>.</li><li>5. Adhere to the safe use condition: Communicate with the pharmacy to confirm completion of pregnancy testing.</li></ol>
Before dispensing	<ol style="list-style-type: none"><li>6. Receive counseling from the pharmacy or the prescriber who dispenses Adempas on the risk of embryo-fetal toxicity, the need for effective contraception during treatment and for one month after stopping treatment, to get monthly pregnancy tests, and to report a pregnancy immediately.</li><li>7. Get a pregnancy test.</li><li>8. Adhere to the safe use condition: Communicate with the pharmacy to confirm completion of pregnancy testing.</li></ol>
During treatment and after treatment discontinuation for one month	<ol style="list-style-type: none"><li>9. Adhere to the safe use condition: Use effective contraception as described in the <a href="#">Guide for Female Patients</a>.</li><li>10. Agree to be contacted by the manufacturer if you become pregnant.</li></ol>
After treatment discontinuation; one month	<ol style="list-style-type: none"><li>11. Get a pregnancy test.</li></ol>
At all times	<ol style="list-style-type: none"><li>12. Inform the prescriber immediately if you miss a menstrual period or suspect a pregnancy.</li></ol>

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## 3. Pre-pubertal females who are prescribed Adempas:

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Before treatment initiation	<ol style="list-style-type: none"><li>1. Review the <a href="#">Guide for Female Patients</a>.</li><li>2. Enroll in the REMS Program by completing the <a href="#">Patient Enrollment and Consent Form</a> with the prescriber. Enrollment information will be provided to the REMS Program.</li><li>3. Receive counseling from the prescriber on the risk of embryo-fetal toxicity and to immediately contact your prescriber if you begin to menstruate using the <a href="#">Guide for Female Patients</a>.</li></ol>
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| At all times | <ol style="list-style-type: none"><li>If over the age of 8: Be monitored for a change in reproductive status.</li><li>Inform the prescriber if there is change in reproductive status.</li></ol> |
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**4. Post-menopausal females or females with other medical reason for permanent, irreversible infertility who are prescribed Adempas:**

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| Before treatment initiation | <ol style="list-style-type: none"><li>Review the <a href="#">Guide for Female Patients</a>.</li><li>Enroll in the REMS Program by completing the <a href="#">Patient Enrollment and Consent Form</a> with the prescriber. Enrollment information will be provided to the REMS Program.</li></ol> |
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| At all times | <ol style="list-style-type: none"><li>Inform the prescriber if there is a change in your reproductive status.</li></ol> |
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**5. Outpatient Pharmacies and prescribers that dispense Adempas must:**

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| To become certified to dispense | <ol style="list-style-type: none"><li>For outpatient pharmacies: Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the outpatient pharmacy.</li><li>For prescribers who dispense: Complete the certified dispenser section of the <a href="#">Prescriber Enrollment and Agreement Form</a>.</li><li>Review the <a href="#">Prescriber and Pharmacy Guide</a>.</li><li>Train all relevant staff involved in dispensing on the Adempas REMS Program requirements, procedures, and REMS materials using the <a href="#">Prescriber and Pharmacy Guide</a>.</li><li>Establish processes and procedures to verify the female patient is enrolled, the reproductive status of the patient has not changed, the prescriber is certified, and if the prescriber dispensed a 30 days' supply of Adempas.</li><li>For females of reproductive potential: Establish processes and procedures to verify that pregnancy testing is complete or the prescriber authorizes the refill through the processes and procedures established as a requirement of the REMS program.</li></ol> |
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| Before dispensing | <ol style="list-style-type: none"><li>7. For females of reproductive potential: Counsel the patient on the risk of embryo-fetal toxicity, the need to use effective contraception during treatment and for one month after stopping treatment, to get monthly pregnancy tests, and inform her prescriber immediately if she misses a menstrual period or suspects she may be pregnant.</li><li>8. Verify the female patient is enrolled, the reproductive status has not changed, the prescriber is certified, and if the prescriber dispensed a 30 days' supply of Adempas through the processes and procedures established as a requirement of the REMS Program.</li><li>9. For females of reproductive potential: Verify that pregnancy testing is complete or the prescriber authorizes the refill through the processes and procedures established as a requirement of the REMS Program.</li><li>10. For females of reproductive potential: Dispense no more than a 30-days' supply.</li><li>11. For prescribers who dispense: Report dispensing Adempas to the REMS Program using the <a href="#">Patient Enrollment and Consent Form</a>.</li></ol> |
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| At all times | <ol style="list-style-type: none"><li>12. Report pregnancies to Bayer HealthCare Pharmaceuticals, Inc.</li><li>13. Not distribute, transfer, loan, or sell Adempas.</li><li>14. For outpatient pharmacies: Maintain and submit records of daily product dispensing data for females of reproductive potential.</li><li>15. Maintain records of all processes and procedures including compliance with those processes and procedures.</li><li>16. Comply with audits carried out by the manufacturer or a third party acting on behalf of the manufacturer to ensure that all processes and procedures are in place and are being followed.</li></ol> |
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**6. Inpatient Pharmacies that dispense Adempas must:**

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To become certified to dispense	<ol style="list-style-type: none"> <li>1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy.</li> <li>2. Have the authorized representative enroll in the REMS Program by completing the <a href="#">Inpatient Pharmacy Enrollment Form</a> and submitting it to the REMS Program.</li> <li>3. Have the authorized representative review the <a href="#">Prescriber and Pharmacy Guide</a>.</li> <li>4. Train all relevant staff involved in dispensing Adempas on the REMS Program requirements, procedures and REMS materials using the <a href="#">Prescriber and Pharmacy Guide</a>.</li> <li>5. Establish processes and procedures to verify the female patient is enrolled in the REMS Program or will be enrolled prior to discharge, her reproductive status, and the female patient is under the supervision and care of a certified prescriber.</li> <li>6. For females of reproductive potential: establish processes and procedures to verify pregnancy testing is complete and that the patient is counseled on the risk of embryo-fetal toxicity, the need to use effective contraception, to get monthly pregnancy tests, and to inform the prescriber of a pregnancy immediately.</li> </ol>
Before dispensing	<ol style="list-style-type: none"> <li>7. Verify the female patient is under the supervision and care of a certified prescriber, her reproductive status, and that she is enrolled or will be enrolled in the REMS Program prior to discharge through the processes and procedures established as a requirement of the REMS Program.</li> <li>8. For females of reproductive potential: Verify pregnancy testing is complete, and that the patient is counseled on the risk of embryo-fetal toxicity, the need to use effective contraception, to get monthly pregnancy tests, and to inform the prescriber of a pregnancy immediately through the processes and procedures established as a requirement of the REMS Program.</li> </ol>
At discharge	<ol style="list-style-type: none"> <li>9. Verify female patient is enrolled in the REMS Program through the processes and procedures established as a requirement of the REMS.</li> <li>10. Dispense no more than a 15-day's supply.</li> </ol>
At all times	<ol style="list-style-type: none"> <li>11. Report pregnancies to Bayer HealthCare Pharmaceuticals, Inc.</li> <li>12. Not distribute, transfer, loan, or sell Adempas.</li> <li>13. Maintain records of all processes and procedures including compliance with those processes and procedures.</li> <li>14. Comply with audits carried out by the manufacturer or a third party acting on behalf of the manufacturer to ensure that all processes and procedures are in place and are being followed.</li> </ol>

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**7. Wholesalers-distributors that distribute Adempas must:**

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To be able to distribute	<ol style="list-style-type: none"> <li>1. Establish processes and procedures to ensure that the drug is distributed only to certified pharmacies and certified prescribers who can dispense Adempas.</li> <li>2. Train all relevant staff involved in distribution on the Adempas REMS Program requirement.</li> </ol>
At all times	<ol style="list-style-type: none"> <li>3. Distribute only to certified pharmacies and certified prescribers who can dispense Adempas.</li> <li>4. Maintain records of drug distribution.</li> <li>5. Comply with audits carried out by the manufacturer or a third party acting on behalf of the manufacturer to ensure that all processes and procedures are in place and are being followed.</li> </ol>

**Bayer HealthCare Pharmaceuticals, Inc must provide training to healthcare providers who prescribe Adempas.**

The training includes the following educational material: [Prescriber and Pharmacy Guide](#). The training must be available online or by calling the REMS Program.

**Bayer HealthCare Pharmaceuticals, Inc must provide training to pharmacies that dispense Adempas.**

The training includes the following educational materials: [Prescriber and Pharmacy Guide](#). The training must be available online or by calling the REMS Program.

**To support REMS Program operations, Bayer HealthCare Pharmaceuticals, Inc must:**

1. Establish and maintain a REMS Program website, [www.AdempasREMS.com](http://www.AdempasREMS.com). The REMS Program website must include the capability to complete prescriber and inpatient pharmacy certification or enrollment online, the capability to enroll and manage patients online, and the option to print the Prescribing Information, Medication Guide, and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program website. The REMS Program website must not link back to the promotional product website.
2. Make the REMS Program website fully operational and all REMS materials available through the REMS Program website or coordinating center within 90 calendar days of REMS modification approval (MM/YYYY).
3. Establish and maintain a REMS Program coordinating center for REMS participants at 1-866-228-3546.
4. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the Adempas REMS Program.
5. Ensure prescribers are able to certify by submitting a completed [Prescriber Enrollment and Agreement Form](#) by fax, online and phone.
6. Ensure outpatient pharmacies are able to certify by contracting with the manufacturer and agreeing to comply with the requirements of the REMS Program.
7. Ensure inpatient pharmacies are able to certify by submitting a completed [Inpatient Pharmacy Enrollment Form](#) by fax, online and phone.
8. Ensure prescribers are able to report change in reproductive status by fax and online.
9. Ensure prescribers are able to complete the patient enrollment process by fax and online.

10. Ensure pharmacies are able to confirm patient enrollment, prescriber certification, and safe use conditions are met prior to dispensing Adempas by phone and online.
11. Ensure prescribers are able to report dispensing Adempas by fax and online.
12. Ensure pharmacies are able to enroll as inpatient (including, but not limited to, pharmacies in hospitals, long-term care facilities, and prisons) or as outpatient pharmacies.
13. Ensure pharmacies are able to confirm by phone and online if Adempas was dispensed by a prescriber.
14. Ensure inpatient pharmacies are able to contact the coordinating center for assistance in obtaining up to a 15 day supply of drug for a specific inpatient while the inpatient pharmacy completes the certification process.
15. Provide the [Prescriber Enrollment and Agreement Form](#) and [Prescriber and Pharmacy Guide](#) to prescribers who (1) attempt to prescribe Adempas and are not yet certified or (2) inquire about how to become certified.
16. Notify certified pharmacies of a patient's change or misclassification in reproductive status within one business day of receipt of a completed [Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form](#).
17. Provide certified prescribers access to the database of certified pharmacies and enrolled patients.
18. Provide certified pharmacies access to the database of certified prescribers and enrolled patients.

**To ensure REMS participants' compliance with the REMS Program, Bayer HealthCare Pharmaceuticals, Inc must:**

19. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: Adempas distribution and dispensing; certification of prescribers and pharmacies; enrolled patients; and audits of REMS pharmacies, prescribers who dispense, and wholesalers-distributors. These records must be readily available for FDA inspections.
20. Establish a plan for addressing noncompliance with REMS Program requirements.
21. Monitor prescribers, pharmacies, and wholesalers-distributors on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if noncompliance is identified, including de-certification.
22. Audit all certified outpatient pharmacies and prescribers who dispense within 180 days after they become certified, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements.
23. Audit all wholesalers-distributors within 180 days after they become authorized to distribute, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements.
24. Audit all certified outpatient pharmacies, wholesalers-distributors, the coordinating center for Adempas, at least 10% of certified inpatient pharmacies that have ordered Adempas annually and, audit, every 6 months, all prescribers who dispense to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements.
25. Take reasonable steps to improve operation of and compliance with the requirements in the Adempas REMS Program based on monitoring and evaluation of the Adempas REMS Program.

## IV. REMS Assessment Timetable

Bayer HealthCare Pharmaceuticals, Inc must submit REMS Assessments at 6 months and 12 months from the date of the initial REMS approval (10/18/2013), and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Bayer HealthCare Pharmaceuticals, Inc must submit each assessment so that it will be received by the FDA on or before the due date.

## V. REMS Materials

The following materials are part of the Adempas REMS:

### Enrollment Forms

Prescriber:

1. [Prescriber Enrollment and Agreement Form](#)

Patient:

2. [Patient Enrollment and Consent Form](#)

Pharmacy:

3. [Inpatient Pharmacy Enrollment Form](#)

### Training and Educational Materials

Prescriber:

4. [Prescriber and Pharmacy Guide](#)

Patient:

5. [Guide for Female Patients](#)

Pharmacy:

6. [Prescriber and Pharmacy Guide](#)

### Patient Care Form

7. [Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form](#)

### Other Materials

8. [REMS Program website \(www.AdempasREMS.com\)](http://www.AdempasREMS.com)