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I. Adempas REMS (Risk Evaluation and Mitigation Strategy) Program

INDICATIONS
Adempas® (riociguat) is a soluble guanylate cyclase (sGC) stimulator indicated for the treatment of adults with:

- Persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class.
- Pulmonary Arterial Hypertension (PAH) (WHO Group 1) to improve exercise capacity, improve WHO functional class and to delay clinical worsening.

Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).

RISK OF TERATOGENICITY
Adempas is contraindicated in females who are pregnant. Adempas may cause fetal harm when administered to a pregnant woman. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. To prevent pregnancy, females of reproductive potential must use reliable contraception during treatment and for one month after stopping Adempas. Patients must not become pregnant while taking Adempas.

ADEMPAS REMS PROGRAM
A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug and is required by the US Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks.

Bayer Pharmaceuticals has worked with the FDA to develop the Adempas REMS Program to educate prescribers about the risk of teratogenicity. The REMS requires that females be enrolled in the Adempas REMS Program in order to receive Adempas.

The goals of the Adempas REMS Program are:

1. To inform prescribers, patients, and pharmacists about the serious risk of teratogenicity and safe-use conditions for Adempas
2. To minimize the risk of fetal exposure and adverse fetal outcomes in Females of Reproductive Potential prescribed Adempas
   a. Females who are pregnant must not be prescribed Adempas
   b. Females taking Adempas must not become pregnant
II. Overview of the Adempas REMS Program

Because of the risk of teratogenicity, Adempas is available only through the Adempas REMS Program, which includes restricted distribution of Adempas.

The required components of the Adempas REMS Program are:

- Healthcare providers (prescribers) who prescribe Adempas must:
  - enroll in the program, and comply with the REMS requirements
  - educate and counsel Females of Reproductive Potential on the risks of Adempas, including the risk of serious birth defects
  - order and review pregnancy tests for Females of Reproductive Potential prior to initiation of treatment, monthly during treatment, and for one month after stopping treatment
  - report any change or misclassification in a female’s reproductive status to the Adempas REMS Program

- Healthcare providers must enroll all female patients in the Adempas REMS Program after determining whether she is a Female of Reproductive Potential or a Female of Non-Reproductive Potential.

Definitions of Reproductive Potential Status

Females of Reproductive Potential
- Females of reproductive potential include girls who have entered puberty and all females who have a uterus and have not passed through menopause (as defined below).
- For the purposes of this REMS, puberty includes those girls who are at least Tanner Stage 3 and have not yet had a menses (premenarchal).

Females of Non-Reproductive Potential
- Pre-Pubertal Females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential
- Post-Menopausal Females: Females who have passed through menopause. Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or post-surgical from bilateral oophorectomy.
- Females with other medical reasons for permanent, irreversible infertility.

- For Females of Reproductive Potential
  - pregnancy must be ruled out prior to drug initiation, monthly during treatment, and one month after stopping treatment
  - she must agree to be contacted by Bayer if she becomes pregnant either while on Adempas or within one month of treatment discontinuation

- Only certified outpatient pharmacies that agree to follow the Adempas REMS Program requirements via contract will dispense Adempas to outpatients.

Only certified inpatient pharmacies that agree to follow the Adempas REMS Program requirements will stock Adempas for inpatient use.
III. Summary of the Adempas REMS Program

All prescribers must be enrolled in the Adempas REMS Program. To become enrolled, a healthcare provider must complete an Adempas REMS Prescriber Enrollment and Agreement Form to the Adempas REMS Program agreeing to follow the Adempas REMS Program requirements. This form must be submitted to the Adempas REMS Program.

All females must be enrolled in the Adempas REMS Program in order to receive Adempas. To become enrolled a patient must complete an Adempas REMS Patient Enrollment and Consent Form with her prescriber. This form must be submitted to the Adempas REMS Program.

Prescribers must determine and document on the Adempas REMS Patient Enrollment and Consent Form whether the patient is a Female of Reproductive Potential, or a Female of Non-Reproductive Potential (Pre-Pubertal Female, Post-Menopausal Female, or a female with other medical reasons for permanent, irreversible infertility). This category must be documented on the Adempas REMS Patient Enrollment and Consent Form. (See Section II for definitions of Reproductive Potential Status).

Based on whether the patient is a Female of Reproductive Potential, a Pre-Pubertal Female, a Post-Menopausal Female, or a female with other medical reasons for permanent, irreversible infertility, the prescriber must perform certain actions before initiating treatment, during treatment, and after the patient stops taking Adempas.

### Summary of Adempas REMS Program Requirements by Patient Category

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Female of Reproductive Potential</th>
<th>Female of Non-Reproductive Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Pubertal</td>
<td>Post-Menopausal</td>
</tr>
<tr>
<td>Prescriber enrolls female patients into the Adempas REMS Program</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Counseling with the Adempas REMS Guide for Females Who Can Get Pregnant</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Counseling with the Adempas Medication Guide, including the risk of teratogenicity</td>
<td>X</td>
<td>X*</td>
</tr>
<tr>
<td>Prescriber must order and review pregnancy tests prior to initiation of treatment, monthly during treatment, and for one month after stopping treatment</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Prescriber must verify reproductive status annually by completing the Adempas REMS Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form for females who are at least 8 years of age and older</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Prescriber must complete the Adempas REMS Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form upon becoming aware of any change or misclassification in reproductive status within 10 business days of awareness</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*Counsel Pre-Pubertal Female patient and/or a parent/guardian
Prescribers must complete the following steps in the Adempas REMS Program:

1. **Enroll in the Adempas REMS Program**
   - Prior to writing an Adempas prescription for a patient, a healthcare provider must enroll in the Adempas REMS Program.
     - **Read** the Adempas Prescribing Information (PI), Adempas Medication Guide, and the Prescriber and Pharmacy Guide for the Adempas REMS Program Guide for the Adempas REMS Program (this guide) to understand the risks of Adempas and the Adempas REMS Program requirements.
     - **Agree** to follow the Adempas REMS Program requirements by completing and submitting an Adempas REMS Prescriber Enrollment and Agreement Form to the Adempas REMS Program.
     - **Receive** an enrollment confirmation from the Adempas REMS Program verifying that certification has been completed. Prescribers can access the program materials at [www.adempasREMS.com](http://www.adempasREMS.com).

2. **Determine the Reproductive Status of Female Patients**
   (See definitions in Section II: Overview of the Adempas REMS Program).

3. **Educate and Counsel Patients**
   - For all females, prescribers must:
     - Advise the patient that Adempas is only available through a restricted distribution program called the Adempas REMS Program.
     - Educate and counsel patients about the risks of Adempas
       - For Females of Reproductive Potential, prescribers must:
         - Educate her about the risk of teratogenicity; the need to use reliable contraception during Adempas treatment and for one month following treatment discontinuation; and her medical options in the event of unprotected sexual intercourse or known or suspected contraception failure.
         - Advise the patient of the requirement for initial and monthly pregnancy tests to confirm they are not pregnant, so they can begin and continue to receive Adempas.
         - Provide ongoing counseling on the importance of using reliable contraception during Adempas treatment and for one month after stopping treatment.
         - Counsel her to immediately contact her healthcare provider if she misses a menstrual period or suspects she is pregnant.
         - Counsel her that she must agree to be contacted prior to each shipment to confirm that a pregnancy test has been completed.
• For Females of Non-Reproductive Potential
  o For a Post-Menopausal Female or a female with other medical reasons for permanent, irreversible infertility, prescribers must:
    • Provide the Adempas Medication Guide to each and instruct her to read it.
  o For Pre-Pubertal Females, prescribers must:
    • Review with her and a parent/guardian the Adempas Medication Guide.
    • Educate her and a parent/guardian about the risk of teratogenicity.
    • Counsel her and a parent/guardian to immediately contact her healthcare provider if she gets her menstrual period.

• Prescribers must counsel any patient who fails to comply with the program requirements.

4. Check Pregnancy Status
   (in Females of Reproductive Potential)
   • Order a pregnancy test.
   • Review the pregnancy test results prior to the initiation of Adempas to ensure the result is negative.
   • Notify the patient of negative pregnancy test results prior to the initiation of Adempas.

5. Enroll Female Patients in the Adempas REMS Program
   • All female patients must be enrolled in the Adempas REMS Program in order to receive Adempas.
   • Confirm that the patient has agreed to comply with the Adempas REMS Program requirements.
   • Complete with the patient the designated section of the Adempas REMS Patient Enrollment and Consent Form and submit it to the Adempas REMS Program.

6. Monitor Patients
   • For Females of Reproductive Potential, prescribers must:
     o Order and review pregnancy tests monthly during treatment with Adempas and for one month after stopping treatment.
     o Notify the patient and Bayer if a patient’s pregnancy test is positive.
     o Monitor patients’ reproductive status during treatment with Adempas and report any changes or misclassifications to the Adempas REMS Program by completing and submitting the Adempas REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form within 10 business days of becoming aware of the change.
   • For Females of Non-Reproductive Potential, prescribers must:
     o Monitor patients’ reproductive status during treatment with Adempas and report any changes or misclassifications to the Adempas REMS Program by completing and submitting the Adempas REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form within 10 business days of becoming aware of the change.
     o For each Pre-Pubertal Female who is at least 8 years of age and older, annually verify and report the reproductive status by completing and submitting the Adempas REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form.

7. Report Pregnancies
   • Prescribers must also report as soon as possible any pregnancies associated with the use of Adempas to Bayer at 1-888-842-2937, or send the information to DrugSafety. GPV.US@bayer.com.
V. Contraceptive Options for Females of Reproductive Potential

Females of Reproductive Potential must use reliable contraception during treatment and for one month after stopping treatment. The table below indicates the acceptable contraception methods. The patient should be instructed to select one of the below options.

<table>
<thead>
<tr>
<th>OPTION 1</th>
<th>OPTION 2</th>
<th>OPTION 3</th>
<th>OPTION 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>One method from this list:</strong></td>
<td><strong>One method from this list:</strong></td>
<td><strong>One method from this list:</strong></td>
<td><strong>This method:</strong></td>
</tr>
<tr>
<td>Intrauterine system</td>
<td>Estrogen and progesterone oral contraceptives (&quot;the pill&quot;)</td>
<td>Diaphragm with spermicide</td>
<td>Partner’s vasectomy</td>
</tr>
<tr>
<td>LNG-20 IUS-progesterone IUD</td>
<td>Estrogen and progesterone transdermal patch</td>
<td>Cervical cap with spermicide</td>
<td></td>
</tr>
<tr>
<td>LNG-13.5 progesterone IUD</td>
<td>Vaginal ring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard intrauterine device</td>
<td>Progestosterone injection</td>
<td>Male condom</td>
<td>Male condom</td>
</tr>
<tr>
<td>Copper T 380 A IUD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubal sterilization (tie, clip, band, burn)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progesterone implant</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All Females of Reproductive Potential should undergo contraceptive counseling with either the prescriber or another designated healthcare provider trained in contraceptive counseling. Counseling should include a discussion about medical options in the event of unprotected sex or known or suspected contraceptive failure.

If pregnancy is suspected for any reason, a pregnancy test must be performed. The prescriber must notify the Adempas REMS Program of any pregnancies that occur during treatment or within one month after stopping treatment as soon as possible.

Reference ID: 3994854
VI. Role of Certified Pharmacies

Outpatient Pharmacy Dispensing:

Only a limited number of certified pharmacies will dispense Adempas for outpatients. Prior to dispensing Adempas to any female, the pharmacy will confirm that the female and the prescriber who wrote the prescription are enrolled in the Adempas REMS Program. If either the female or prescriber is not enrolled, Adempas will not be dispensed.

Females of Reproductive Potential and Pre-Pubertal Females will only be able to get a 30-day supply of Adempas at one time. The Adempas Medication Guide will be provided to all patients each time Adempas is dispensed.

Females of Reproductive Potential will be contacted each month by the pharmacy to arrange her dispensing of Adempas. The pharmacy will:

- Ask if she has had a pregnancy test within the last month
- Counsel her on the need to use reliable contraception during Adempas treatment and for one month after stopping treatment
- Counsel her to inform her prescriber immediately if she misses a menstrual period, suspects that she may be pregnant, or if her reproductive status changes. All outpatient pharmacists must report any pregnancies associated with the use of Adempas to Bayer at 1-888-842-2937, or send the information to DrugSafety.GPV.US@bayer.com.

Inpatient Pharmacy Dispensing:

Only inpatient pharmacies within institutions such as hospitals, long-term care facilities, and prisons that are certified in the Adempas REMS Program may stock Adempas for patients being treated in the inpatient setting.

As a certified inpatient pharmacy, you must agree to follow the Adempas REMS Program requirements including:

1. Become certified in the Adempas REMS Program
   - Prior to stocking and dispensing Adempas, an authorized representative from the inpatient pharmacy must enroll and be certified in the Adempas REMS Program by completing and submitting an Adempas REMS Inpatient Pharmacy Enrollment Form to the Adempas REMS Program, agreeing to meet all of the steps and requirements outlined in the enrollment form.
     - Bayer may require re-certification of inpatient pharmacies if there are substantive changes to the Adempas REMS Program.

2. Ensure Adempas REMS requirements are met
   - Establish processes and procedures to ensure Adempas REMS requirements are met.
   - Complete training in the Adempas REMS Program by reading the Adempas Prescribing Information, Adempas Medication Guide, and the Prescriber and Pharmacy Guide for the Adempas REMS Program (this guide).
   - Assume responsibility for the training of dispensing staff on the Adempas REMS Program requirements and Adempas REMS materials prior to dispensing Adempas.
   - Agree to audits by the FDA, Bayer, or third party designated by Bayer.
   - Develop a process to track compliance with the Adempas REMS requirements and provide information about your compliance to Bayer upon request.
3. Confirm Inpatient and Prescriber Enrollment in the Adempas REMS Program

- Confirm the inpatient is under the care of a healthcare provider certified in the Adempas REMS Program
- Certified inpatient pharmacies must obtain authorization prior to dispensing Adempas to an inpatient by calling the Adempas REMS Coordinating Center. The Adempas REMS Program will provide authorization to the certified inpatient pharmacy after verifying that the patient and/or prescriber are enrolled (as applicable).
  
  (1) If the patient is new to Adempas treatment the Adempas REMS Coordinating Center will confirm that the prescriber is enrolled in the REMS, and will facilitate patient enrollment into the Adempas REMS Program.
    
  (a) Until the prescriber and/or inpatient are enrolled, you may not dispense Adempas.

  (2) If the patient is continuing Adempas treatment and is a female, the Adempas REMS Coordinating Center will confirm that the female is enrolled in the REMS. If the patient is continuing Adempas, the inpatient prescriber will not need to be enrolled in the REMS.

4. Comply with Dispensing Requirements

- Dispense Adempas only after contacting the Adempas REMS Program Coordinating Center to confirm the REMS requirements are met.
- Do not transfer Adempas to any pharmacy, practitioner, or healthcare setting not certified by the Adempas REMS Program.
- Dispense no more than a 15-day temporary supply of Adempas to any female patient upon discharge from the healthcare facility.

If an inpatient pharmacy needs Adempas and is not certified in the Adempas REMS Program, the inpatient pharmacy can contact the Adempas REMS Program Coordinating Center for assistance in obtaining up to a 15-day supply of Adempas for a specific inpatient while initiating enrollment.

5. Report Pregnancies

- All inpatient pharmacists must report as soon as possible any pregnancies associated with the use of Adempas to Bayer at 1-888-842-2937, or send the information to DrugSafety.GPV.US@bayer.com.

6. Specialty Distributors

- Certified inpatient pharmacies will only be able to purchase Adempas through a limited number of specialty distributors contracted with Bayer.
VII. The Adempas REMS Program Coordinating Center will:

- Process the *Adempas REMS Prescriber Enrollment and Agreement Form*, the *Adempas REMS Patient Enrollment and Consent Form*, and the *Adempas REMS Inpatient Pharmacy Enrollment Form*
- Answer questions for prescribers, patients and pharmacies, as they relate to the Adempas REMS Program
- Monitor compliance with the Adempas REMS Program requirements

The Adempas REMS Program Coordinating Center can be contacted at 1-855-4ADEMPAS (1-855-423-3672), Monday through Friday from 8:00 AM to 8:00 PM EST.

Notes