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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
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 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 (as defined below)

### Definition of 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.

### For Females of Reproductive Potential:
- pregnancy must be ruled out prior to drug initiation and monthly during treatment
- she must agree to be counseled on the requirements of the REMS program and the risks of Adempas
- 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 and submit an Adempas REMS Prescriber Enrollment and Agreement Form to the Adempas REMS Program agreeing to follow the Adempas REMS Program requirements.

All females must be enrolled in the Adempas REMS Program in order to receive Adempas. To become enrolled a patient must complete an Adempas 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 Patient Enrollment and Consent Form whether the patient is a Female of Reproductive Potential, or a Female of Non-Reproductive Potential (Pre-Pubertal Female or Post-Menopausal Female). This category must be documented on the Adempas 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, or a Post-Menopausal Female, 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></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 Reproductive Potential Status Form for females who are at least 8 years of age and older</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Prescriber must complete the Adempas REMS Reproductive Potential Status Form upon becoming aware of any change 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 parent/guardian
IV. your Role in the Adempas REMS Program

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 Full Prescribing Information (PI), Adempas Medication Guide, and the Prescriber 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.

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.
For Females of Non-Reproductive Potential, prescribers must:
- Provide the *Adempas Medication Guide* to each Post-Menopausal Female and instruct her to read it.
- For Pre-Pubertal Females, prescribers must:
  - Review with her and her parent/guardian the *Adempas Medication Guide*.
  - Educate her and her parent/guardian about the risk of teratogenicity.
  - Counsel her and her 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 Patient Enrollment and Consent Form* and submit it to the Adempas REMS Program.

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

### 7. Report Pregnancies
- Prescribers must also report any pregnancies associated with the use of Adempas to Bayer at 1-888-842-2937, or send the information to DrugSafety.
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.

**Option 1**
- Intrauterine system
  - LNG-20 IUS-progesterone IUD
  - LNG-13.5 progesterone IUD
- Standard intrauterine device
  - Copper T 380 A IUD
- Tubal sterilization (tie, clip, band, burn)
- Progesterone implant

**Option 2**
- One method from this list:
  - Estrogen and progesterone oral contraceptives ("the pill")
  - Estrogen and progesterone transdermal patch
  - Vaginal ring
  - Progesterone injection

**Option 3**
- One method from this list:
  - Diaphragm with spermicide
  - Cervical cap with spermicide

**Option 4**
- This method:
  - Partner's vasectomy

**Option 1 + Option 2**
- One method from this list:
  - Male condom
  - Diaphragm with spermicide
  - Cervical cap with spermicide

**Option 3 + Option 4**
- This method:
  - Male condom

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.

Reference ID: 3522688
VI. Role of Certified Pharmacies

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

Inpatient Pharmacy dispensing:

Only inpatient pharmacies within institutions such as hospitals, long-term care facilities, prisons, and state psychiatric units that are certified in the Adempas REMS Program may stock Adempas for patients being treated in the inpatient setting. Inpatient pharmacies may not dispense more than a 15-day temporary supply of Adempas to any patient upon discharge from the healthcare facility. Bayer will ensure that 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 for certification.

VII. The Adempas REMS Program Coordinating Center

The Adempas REMS Program Coordinating Center will:

- Process the Adempas REMS Prescriber Enrollment and Agreement Form and the Adempas Patient Enrollment and Consent 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.