

ADEMPAS[®] REMS (RISK EVALUATION AND MITIGATION STRATEGY)



Prescriber and Pharmacy Guide for the Adempas REMS

Changes to the Adempas Risk Evaluation and Mitigation Strategy (REMS) February 2020

- Revised Form: Adempas REMS Patient and Enrollment and Consent Form
- Revised Form: Adempas REMS Prescriber Enrollment and Agreement Form

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I. Adempas REMS (Risk Evaluation and Mitigation Strategy)

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 EMBRYO-FETAL TOXICITY

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 effective contraception during treatment and for one month after stopping Adempas. Patients must not become pregnant while taking Adempas.

ADEMPAS REMS

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 to educate prescribers about the risk of embryo-fetal toxicity. The REMS requires that females be enrolled in the Adempas REMS in order to receive Adempas.

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

1. Ensuring prescribers are educated on the following:

- the risks of embryo-fetal toxicity

2. Ensuring prescribers are educated on and adhere to the following:

- counseling patients about these risks and the need for monthly monitoring
- enrolling patients in the Adempas REMS
- monitoring patients at baseline and monthly

3. Ensuring that pharmacies are educated on the following:

- the risks 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 risks of embryo-fetal toxicity
- appropriate baseline and monthly patient monitoring
- appropriate contraception

II. Overview of the Adempas REMS

Because of the risk of embryo-fetal toxicity, Adempas is available only through the Adempas REMS, which includes restricted distribution of Adempas.

Therequired components of the Adempas REMS 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 before the start 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
- Healthcare providers must enroll all female patients in the Adempas REMS 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 before the start of treatment, 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 requirements via contract will dispense Adempas to outpatients.
 - Only certified inpatient pharmacies that agree to follow the Adempas REMS requirements will stock Adempas for inpatient use.
 - Only certified prescribers dispensing Adempas that agree to follow the Adempas REMS requirements will be eligible to obtain and dispense Adempas to patients. New and existing prescribers who wish to dispense Adempas must agree to these requirements by completing and signing the **Prescriber Enrollment and Agreement Form**.

III. Summary of the Adempas REMS

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

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

Prescribers must determine and document on the *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 *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 Requirements by Patient Category

Requirement	Female of Reproductive Potential	Female of Non-Reproductive Potential		
		Pre-Pubertal	Post-Menopausal	Other medical reasons for permanent, irreversible infertility
Prescriber enrolls female patients into the Adempas REMS	X	X	X	X
Counseling with the <i>Guide for Female Patients</i>	X	X*		
Prescriber must order and review pregnancy tests before the start of treatment, monthly during treatment, and for one month after stopping treatment	X			
Prescriber must verify reproductive status annually by completing the <i>Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form</i> for females who are at least 8 years of age and older		X		
Prescriber must complete the <i>Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form</i> upon becoming aware of any change or misclassification in reproductive status within 10 business days of awareness	X	X	X	X

*Counsel Pre-Pubertal Female patient and/or a parent/guardian

IV. Prescriber's Role in the Adempas

Prescribers must complete the following steps in the Adempas REMS:

1. Enroll in the Adempas REMS

- Prior to writing an Adempas prescription for a patient, a healthcare provider must enroll in the Adempas REMS.
 - **Read** the *Adempas Prescribing Information (PI)* and the *Prescriber and Pharmacy Guide* (this guide) to understand the risks of Adempas and the Adempas REMS requirements.
 - **Agree** to follow the Adempas REMS requirements by completing and submitting an *Prescriber Enrollment and Agreement Form* to the Adempas REMS.
 - **Receive** an enrollment confirmation from the Adempas REMS 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).

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.
 - Assess the patient's reproductive status using the definitions in the *Prescriber and Pharmacy Guide*. Document and submit the results to the REMS using the Patient Enrollment Form
- For Females of Reproductive Potential, prescribers must:
 - Review with her the *Guide for Female Patients*.
 - 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, her medical options in the event of unprotected sexual intercourse or known or suspected contraception failure, and to immediately contact her healthcare provider if she misses a menstrual period or suspects that she is pregnant using the *Guide for Female Patients*.

- 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.
 - Counsel the patient if she is not complying with the required testing or if she is not using effective contraception.
 - 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
 - For a Post-Menopausal Female or a female with other medical reasons for permanent, irreversible infertility, prescribers must:
 - Provide the *Guide for Female Patients* and instruct her to read it.
 - For Pre-Pubertal Females, prescribers must:
 - Review with her and a parent/guardian the *Guide for Female Patients*.
 - Counsel her and a parent/guardian about the risk of embryo-fetal toxicity.
 - 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 before the start of treatment with 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

- All female patients must be enrolled in the Adempas REMS in order to receive Adempas.
- Confirm that the patient has agreed to comply with the Adempas REMS requirements.
- Complete with the patient the designated sections of the *Patient Enrollment and Consent Form* and submit it to the Adempas REMS.

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.
 - Monitor patients' reproductive status during treatment with Adempas and report any changes or misclassifications to the Adempas REMS by completing and submitting the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change.

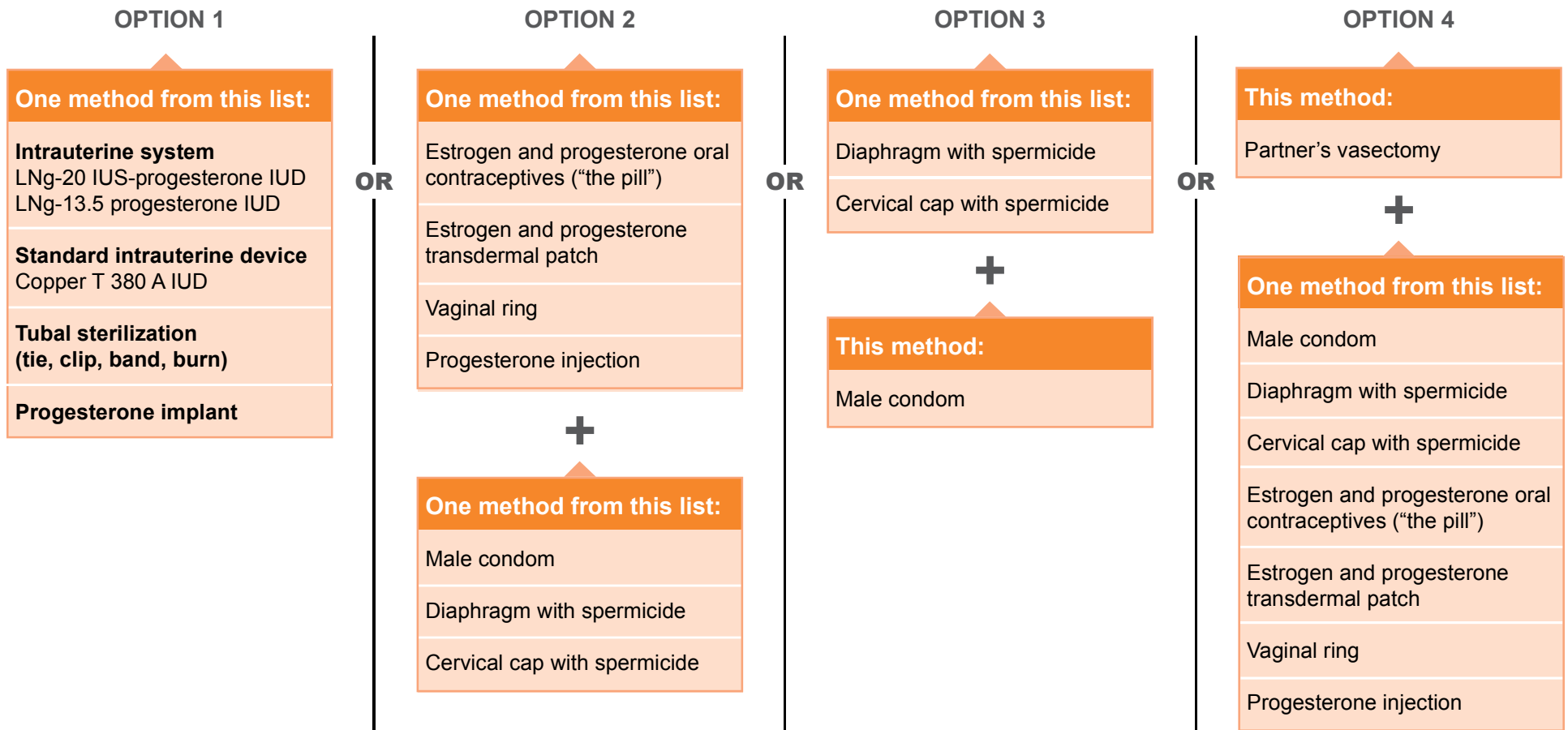
- For Females of Non-Reproductive Potential, prescribers must:
 - Monitor patients' reproductive status during treatment with Adempas and report any changes or misclassifications to the Adempas REMS by completing and submitting the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change.
 - 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 *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 effective 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.



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 of any pregnancies that occur during treatment or within one month after stopping treatment as soon as possible.

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. If either the female or prescriber is not enrolled, Adempas will not be dispensed.

For all female patients, outpatient pharmacies will:

- Contact the Adempas REMS Coordinating Center to determine if the patient has received medication from the prescriber.
- 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 processes and procedures established as a requirement of the REMS.

For Females of Reproductive Potential, outpatient pharmacies will:

- Counsel her on the risk of embryo-fetal toxicity
- Contact her each month to arrange the dispensing of Adempas
- Ask if she has had a pregnancy test within the last month or the prescriber has authorized the refill
- Counsel her on the need to use effective contraception during Adempas treatment and for one month after stopping treatment
- Counsel her to get monthly pregnancy tests
- Counsel her to inform her prescriber immediately if she misses a menstrual period or suspects that she may be pregnant
- Verify reproductive status has not changed
- Dispense no more than a 30-days' supply

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.

Females of Reproductive Potential will only be able to get a 30-day supply of Adempas at one time.

Inpatient Pharmacy Dispensing:

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

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

1. Become certified in the Adempas REMS

- Prior to stocking and dispensing Adempas, an authorized representative from the inpatient pharmacy must enroll and be certified in the Adempas REMS by completing and submitting an *Inpatient Pharmacy Enrollment Form* to the Adempas REMS, 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.

2. Ensure Adempas REMS requirements are met

- establish processes and procedures to ensure Adempas REMS requirements are met
- maintain records that all processes and procedures are in place and are being followed
- complete training in the Adempas REMS by reading the *Prescriber and Pharmacy Guide* (this guide)
- assume responsibility for the training of all relevant staff in dispensing Adempas REMS requirements, procedures, and Adempas REMS materials prior to dispensing Adempas, using the *Prescriber and Pharmacy Guide*
- establish processes and procedures to verify the female patient is enrolled in the REMS or will be enrolled prior to discharge, her reproductive status, and the female patient is under the supervision and care of a certified prescriber
- 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

3. Confirm Inpatient and Prescriber Enrollment in the Adempas REMS

- 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 prior to discharge through the processes and procedures established as a requirement of the REMS.
- 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.
- at discharge, verify female patient is enrolled in the REMS through the processes and procedures established as a requirement of the REMS

4. Comply with Dispensing Requirements

- do not distribute, transfer, loan, or sell Adempas
- comply with audits by the manufacturer or a third party acting on behalf of the manufacturer to ensure all processes and procedures are in place and being followed
- dispense no more than a 15-day temporary supply of Adempas to any female patient upon discharge from the healthcare facility

5. Report Pregnancies

- All inpatient 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.

6. Purchase Adempas through Specialty Distributors

- Certified inpatient pharmacies will only be able to purchase Adempas through a limited number of specialty distributors contracted with Bayer.

