Package Leaflet: Information for the user

Adempas 0.5 mg film-coated tablets
Adempas 1 mg film-coated tablets
Adempas 1.5 mg film-coated tablets
Adempas 2 mg film-coated tablets
Adempas 2.5 mg film-coated tablets

riociguat

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Adempas is and what it is used for

Adempas contains the active substance riociguat. Riociguat is a type of medicine called a guanylate cyclase (sGC)-stimulator. It works by widening the pulmonary arteries (the blood vessels that connect the heart to the lungs), making it easier for the heart to pump blood through the lungs. Adempas can be used to treat adults with certain forms of pulmonary hypertension, a condition in which these blood vessels become narrowed, making it harder for the heart to pump blood through them and leading to high blood pressure in the vessels. Because the heart must work harder than normal, people with pulmonary hypertension feel tired, dizzy and short of breath. By widening the narrowed arteries, Adempas leads to an improvement in your ability to carry out physical activity.

Adempas is used in either of two types of pulmonary hypertension:

- **chronic thromboembolic pulmonary hypertension (CTEPH)**.
  In CTEPH, the blood vessels of the lung are blocked or narrowed with blood clots. Adempas can be used for patients with CTEPH who cannot be operated on, or after surgery for patients in whom increased blood pressure in the lungs remains or returns.
- **certain types of pulmonary arterial hypertension (PAH)**.
  In PAH, the wall of the blood vessels of the lungs are thickened and the vessels become narrowed. Adempas is only prescribed for certain forms of PAH, i.e. idiopathic PAH (the cause of PAH is unknown), heritable PAH and PAH caused by connective tissue disease. Your doctor will check this. Adempas can be taken alone or together with certain other medicines used to treat PAH.

2. What you need to know before you take Adempas

Do not take Adempas:
- if you are taking certain medicines called **PDE5 inhibitors** (e.g. sildenafil, tadalafil, vardenafil). These are medicines used for the treatment of high blood pressure in the arteries of the lungs (PAH) or erectile dysfunction.
- if you have **severe liver problems** (severe hepatic impairment, Child Pugh C).
- if you are **allergic** to riociguat or any of the other ingredients of this medicine (listed in section 6).
- if you are **pregnant.**
- if you are taking **nitrates** or **nitric oxide donors** (such as amyl nitrite) in any form, medicines often used to treat high blood pressure, chest pain or heart disease. This also includes recreational drugs called poppers.
- if you have **low blood pressure** (systolic blood pressure less than 95 mmHg) before starting first treatment with this medicine.
- if you have increased pressure in your pulmonary circulation associated with scarring of the lungs, of unknown cause (idiopathic pulmonary pneumonia).

If any of these applies to you, **talk to your doctor first** and do not take Adempas.

Warnings and precautions
Talk to your doctor or pharmacist before taking Adempas if:
- you have recently experienced serious **bleeding from the lung**, or if you have undergone treatment to stop **coughing up blood** (bronchial arterial embolisation).
- you take **blood-thinning medicines** (anticoagulants) since this may cause bleeding from the lungs. Your doctor will regularly monitor you.
- you feel **short of breath** during treatment with this medicine, this can be caused by a build-up of fluid in the lungs. Talk to your doctor if this happens.
- you have any symptoms of **low blood pressure** (hypotension) such as dizziness, lightheadedness, or fainting or if you are taking medicines to lower your blood pressure or medicines that cause an increase in urination or if you have problems with your heart or circulation. Your doctor may decide to monitor your blood pressure. If you are older than 65 years, you have an increased risk of developing low blood pressure.
- you take medicines used to **treat fungal infections** (e.g. ketoconazole, posaconazole, itraconazole) or medicines for the **treatment of HIV infection** (e.g. abacavir, atazanavir, cobicistat, darunavir, dolutegravir, efavirenz, elvitegravir, emtricitabine, lamivudine, rilpivirine, ritonavir, and tenofovir). Your doctor will monitor your health status and should consider a reduced starting dose for Adempas.
- your **kidneys do not work properly** (creatinine clearance < 30 ml/min) or if you are **on dialysis** as the use of this medicine is not recommended.
- you have **moderate liver problems** (hepatic impairment, Child Pugh B).
- you start or stop **smoking** during treatment with this medicine, because this may influence the level of riociguat in your blood.

You will receive Adempas only for special types of pulmonary arterial hypertension (PAH), see section 1. There is no experience in the use of Adempas in other types of PAH. Use of Adempas in other types of PAH is therefore not recommended. Your doctor will check if Adempas is suitable for you.

Children and adolescents
The use of Adempas in children and adolescents (under 18 years of age) should be avoided because efficacy and safety have not been established for this age group.

Other medicines and Adempas
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, in particular, medicines used for:
- high blood pressure or heart disease (such as nitrates and amyl nitrite) in any form, as you must not take those medicines together with Adempas.
- high blood pressure in the lung vessels (the pulmonary arteries), as you must not take certain medicines (sildenafil and tadalafil) together with Adempas. Other medicines for high blood pressure in the lung vessels (PAH), such as bosentan and iloprost, can be used with Adempas, but you should still tell your doctor.
- erectile dysfunction (such as sildenafil, tadalafil, vardenafil), as you must not take those medicines together with Adempas.
- fungal infections (such as ketoconazole, posaconazole, itraconazole) or HIV infection (such as abacavir, atazanavir, cobicistat, darunavir, dolutegravir, efavirenz, elvitegravir, emtricitabine, rilpivirine or ritonavir) because alternative treatment options may be considered. If you already take one of these medicines and start treatment with Adempas, your doctor will monitor your health status and should consider a reduced starting dose for Adempas.
- epilepsy (e.g. phenytoin, carbamazepine, phenobarbitone).
- depression (St. John's Wort).
- preventing rejection of transplanted organs (ciclosporin).
- joint and muscular pain (niflumic acid).
- cancer (such as erlotinib, gefitinib).
- stomach disease or heartburn (antacids such as aluminium hydroxide/magnesium hydroxide). These antacid medicines should be taken at least two hours before or one hour after taking Adempas.
- nausea, vomiting (feeling or being sick) (such as granisetron).

Smoking
If you smoke, it is recommended that you stop, as smoking may reduce the effectiveness of these tablets. Please tell your doctor if you smoke or if you stop smoking during treatment.

Pregnancy and breast-feeding

Pregnancy
Do not take Adempas during pregnancy. If there is a chance you could become pregnant, use reliable forms of contraception while you are taking these tablets. You are also advised to take monthly pregnancy tests. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Breast-feeding
If you are breast-feeding or planning to breast-feed, ask your doctor or pharmacist for advice before taking this medicine because it might harm your baby. You should not breast-feed while taking this medicine. Your doctor will decide with you if you either should stop breast-feeding or stop treatment with Adempas.

Driving and using machines
Adempas has moderate influence on the ability to drive and use machines. It may cause side effects such as dizziness. You should be aware of the side effects of this medicine before driving or using machines (see section 4).

Adempas contains lactose
If you have been told by a doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Adempas contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium free".

3. How to take Adempas

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Treatment should only be started and monitored by a doctor experienced in the treatment of CTEPH or PAH. During the first weeks of treatment your doctor will need to measure your blood pressure at regular intervals. Adempas is available in different strengths and by checking your blood pressure regularly at the beginning of your treatment, your doctor will ensure that you are taking the appropriate dose.

Crushed tablets:
If you have difficulty swallowing the whole tablet, talk to your doctor about other ways to take Adempas. The tablet may be crushed and mixed with water or a soft food, such as apple sauce, immediately before you take it.

Dose
The recommended starting dose is a 1-mg tablet taken 3 times a day for 2 weeks.
The tablets should be taken 3 times a day, approximately 6 to 8 hours apart. They can generally be taken with or without food.
However, if you are prone to having low blood pressure (hypotension), you should not switch from taking Adempas with food to taking Adempas without food because it may affect how you react to this medicine.

Your doctor will increase the dose every 2 weeks to a maximum of 2.5 mg 3 times a day (maximum daily dose of 7.5 mg) unless you experience any side effects or very low blood pressure. In this case, your doctor will prescribe you Adempas at the highest dose you are comfortable on. For some patients lower doses three times a day might be sufficient, the optimal dose will be selected by your doctor.

Special considerations for patients with kidney or liver problems
You should tell your doctor if you have kidney or liver problems. Your dose may need to be adjusted. If you have severe liver problems (Child Pugh C), do not take Adempas.

65 years or older
If you are 65 years or older your doctor will take extra care in adjusting your dose of Adempas, because you may be at greater risk of low blood pressure.

Special considerations for patients who smoke
You should tell your doctor if you start or stop smoking during treatment with this medicine. Your dose may be adjusted.

If you take more Adempas than you should
If you have taken more tablets than you should and experience any side effects (see section 4), please contact your doctor. If your blood pressure drops (which can make you feel dizzy) then you may need immediate medical attention.

If you forget to take Adempas
Do not take a double dose to make up for a forgotten dose. If you miss a dose, continue with the next dose as planned.

If you stop taking Adempas
Do not stop taking this medicine without talking to your doctor first, because this medicine prevents the progression of the disease. If your treatment has to be stopped for 3 days or more, please tell your doctor before restarting your treatment.

If you are transitioning between sildenafil or tadalafil and Adempas
- If you are stopping sildenafil, you must wait at least 24 hours before you take Adempas.
- If you are stopping tadalafil, you must wait at least 48 hours before you take Adempas.
- If you are stopping Adempas to change to another medicine called a PDE5 inihibitor (e.g. sildenafil or tadalafil) you must wait at least 24 hours from your last dose of Adempas before you take the PDE5 inhibitor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects although not everybody gets them.

The most **serious** side effects are:
- **coughing up blood** (haemoptysis) (common side effect, may affect up to 1 in 10 people),
- **acute bleeding from the lungs** (pulmonary haemorrhage) may result in coughing up blood, cases with fatal outcomes were observed (uncommon side effect, may affect up to 1 in 100 people)**.**

If this happens, **contact your doctor immediately** as you may need urgent medical treatment.

Overall list of possible side effects:

Very common: may affect more than 1 in 10 people
- headache
- dizziness
- indigestion (dyspepsia)
- swelling of limbs (oedema peripheral)
- diarrhoea
- feeling or being sick (nausea and vomiting)

Common: may affect up to 1 in 10 people
- inflammation of the stomach (gastritis)
- inflammation in the digestive system (gastroenteritis)
- reduction of red blood cells (anaemia) seen as pale skin, weakness or breathlessness
- awareness of an irregular, hard, or rapid heartbeat (palpitation)
- low blood pressure (hypotension)
- nose bleed (epistaxis)
- difficulty breathing through your nose (nasal congestion)
- pain in the stomach, intestine or abdomen (gastrointestinal and abdominal pain)
- heartburn (gastro-oesophageal reflux disease)
- difficulty in swallowing (dysphagia)
- constipation
- bloating (abdominal distension)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects, you can help provide more information on the safety of this medicine.

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

Malta
ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal

5. How to store Adempas

Keep this medicine out of the sight and reach of children.

This medicine does not require any special storage conditions.

Do not use this medicine after the expiry date which is stated on the blister and carton after "EXP". The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Adempas contains

- The **active substance** is riociguat.
  Adempas 0.5 mg film-coated tablets
  Each film-coated tablet contains 0.5 mg riociguat.
  Adempas 1 mg film-coated tablets
  Each film-coated tablet contains 1 mg riociguat.
  Adempas 1.5 mg film-coated tablets
  Each film-coated tablet contains 1.5 mg riociguat.
  Adempas 2 mg film-coated tablets
  Each film-coated tablet contains 2 mg riociguat.
  Adempas 2.5 mg film-coated tablets
  Each film-coated tablet contains 2.5 mg riociguat.

- The **other ingredients** are:
  Tablet core: cellulose microcrystalline, crospovidone (type B), hypromellose 5 cP, lactose monohydrate, magnesium stearate and sodium laurilsulfate (see end of section 2 for further information on lactose).
  Film-coat: hydroxypropylcellulose, hypromellose 3 cP, propylene glycol (E 1520) and titanium dioxide (E 171).
  Adempas 1 mg, 1.5 mg tablets also contains iron oxide yellow (E 172).

Adempas 2 mg and 2.5 mg tablets also contains iron oxide yellow (E172) and iron oxide red (E 172).

What Adempas looks like and contents of the pack

Adempas is a film-coated tablet:
Adempas 0.5 mg film-coated tablets
- *0.5 mg tablet:* white, round, biconvex tablets of 6 mm, marked with the Bayer cross on one side and 0.5 and an "R" on the other side.

Adempas 1 mg film-coated tablets
- *1 mg tablet:* pale yellow, round, biconvex tablets of 6 mm, marked with the Bayer cross on one side and 1 and an "R" on the other side.

Adempas 1.5 mg film-coated tablets
- *1.5 mg tablet:* yellow-orange, round, biconvex tablets of 6 mm, marked with the Bayer cross on one side and 1.5 and an "R" on the other side.

Adempas 2 mg film-coated tablets
- *2 mg tablet:* pale orange, round, biconvex tablets of 6 mm, marked with the Bayer cross on one side and 2 and an "R" on the other side.

Adempas 2.5 mg film-coated tablets
- *2.5 mg tablet:* red-orange, round, biconvex tablets of 6 mm, marked with the Bayer cross on one side and 2.5 and an "R" on the other side.

They are available in packs of:
- 42 tablets: two transparent calendar blisters of 21 tablets each.
- 84 tablets: four transparent calendar blisters of 21 tablets each.
- 90 tablets: five transparent blisters of 18 tablets each.
- 294 tablets: fourteen transparent calendar blisters of 21 tablets each.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Bayer AG
51368 Leverkusen
Germany

Manufacturer
Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

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