Adempas® 0.5, 1, 1.5, 2 and 2.5 mg film-coated tablets
(Riociguat)

PRESCRIBING INFORMATION
Refer to Summary of Product Characteristics before prescribing

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in Google Play or Apple App Store. Adverse events should also be reported to MSD, UK (Tel: 0208 154 8000).
By clicking the above link you will leave the MSD website and be taken to the MHRA website.

PRESENTATION
Film-coated tablets containing 0.5, 1, 1.5, 2 or 2.5 mg riociguat

USES
To improve exercise capacity in adults with:
1) chronic thromboembolic pulmonary hypertension (CTEPH): treatment of adult patients with WHO Functional Class (FC) II to III with a. inoperable b. persistent or recurrent after surgery.
2) pulmonary arterial hypertension (PAH) with WHO FC II to III as monotherapy or in combination with endothelin receptor antagonists. Efficacy has been shown in a PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease.

DOSAGE AND ADMINISTRATION
Treatment should be initiated and monitored by a physician experienced in the treatment of CTEPH or PAH ***Adults*****:** Tablets should be taken orally *t.i.d* approx. 6-8 hours apart. Recommended starting dose is 1 mg *t.i.d* for 2 weeks. Increase dose by 0.5 mg *t.i.d* every 2 weeks to max. 2.5 mg *t.i.d,* if systolic blood pressure (SBP) ≥95 mmHg and no signs or symptoms of hypotension. Some PAH patients may reach an adequate response on 6-minute walk distance (6MWD) at a dose of 1.5 mg *t.i.d*. If SBP falls below 95 mmHg, dose should be maintained provided no signs or symptoms of hypotension. If SBP decreases below 95 mmHg during up-titration phase and there are signs or symptoms of hypotension, dose should be decreased by 0.5 mg *t.i.d*. *Maintenance dose* – maintain established dose unless signs and symptoms of hypotension occur. Max. total daily dose is 7.5 mg (i.e., 2.5 mg *t.i.d)*. If a dose is missed, continue treatment with the next dose as planned. If not tolerated, consider dose reduction. Can generally be taken with or without food. Switches between fed and fasted riociguat intake not recommended in patients prone to hypotension. *Treatment discontinuation* – if treatment is interrupted for 3 days or more, restart treatment at 1 mg *t.i.d* for 2 weeks and re-titration dose. ***Children and adolescents*****:** Safety and efficacy have not been established. Non-clinical data show an adverse effect on growing bone. Avoid use in children and in growing adolescents. ***Elderly***: Exercise care during dose titration due to higher risk of hypotension. ***Hepatic impairment*****:** Contraindicated in patients with severe hepatic impairment (Child Pugh C). Patients with mild and moderate hepatic impairment (Child Pugh B) showed a higher exposure to riociguat. Exercise care during dose titration due to higher risk of hypotension. Not recommended in patients with elevated liver aminotransferases or elevated direct bilirubin prior to initiation. ***Renal impairment*****:** Not recommended in patients with severe renal impairment (creatinine clearance <30 mL/min) and for patients on dialysis. Patients with moderate renal impairment (creatinine clearance <50 - 30 mL/min) showed a higher exposure to riociguat. Exercise care during dose titration. ***Stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors:*** consider starting dose of 0.5 mg t.i.d to mitigate the risk of hypotension. Monitor for signs and symptoms of hypotension, if these develop, consider dose reduction for patients on doses ≥1.0 mg. ***Smokers:*** Advise current smokers to stop smoking due to a risk of a lower response. An increase in dose to the max. daily dose of 2.5 mg *t.i.d* may be required in patients who are smoking or start smoking during treatment. A dose decrease may be required in patients who stop smoking.

CONTRA-INDICATIONS
Co-administration with PDE 5 inhibitors; severe hepatic impairment; hypersensitivity to any of the ingredients; pregnancy; co-administration with nitrates or nitric oxide donors in any form (including recreational drugs called 'poppers'); concomitant use with other soluble guanylate cyclase stimulators; patients with SBP < 95 mmHg at treatment initiation; pulmonary hypertension associated with idiopathic interstitial pneumonias.

PRECAUTIONS

Expert assessment of operability with pulmonary endarterectomy should be done prior to treatment of CTEPH with riociguat. Administration of riociguat to patients with pulmonary veno-occlusive disease (PVOD) is not recommended. Signs of pulmonary oedema may be associated with PVOD, consider discontinuing treatment. Carefully monitor PAH patients for respiratory tract bleeding, particularly anticoagulated patients. Avoid use of riociguat in patients with a history of serious haemoptysis or who have previously undergone bronchial arterial embolisation. In case of respiratory tract bleeding, the prescriber should regularly assess the benefit-risk of treatment continuation. Riociguat has vasodilatory properties which may result in lowering of blood pressure, before prescribing, carefully consider whether underlying conditions could be adversely affected by vasodilatory effects. Exercise caution in patients older than 65 years due to increased risk of hypotension. Assess the benefit-risk for each patient prior to concomitant use of riociguat with stable doses of strong multi pathway CYP and P-gp / BCRP inhibitors such as azole antimycotics or HIV protease inhibitors, due to the pronounced increase in riociguat exposure. Initiation of strong multi pathway CYP and P-gp/BCRP inhibitors by patients on stable doses of riociguatis not recommended – consider alternative treatments. Concomitant use of riociguat with strong CYP1A1 inhibitors and strong P-gp / BCRP inhibitors may increase riociguat exposure. These medicinal products should be used with caution. BP should be monitored and dose reduction of riociguat considered. riociguat contains lactose.

Drug Interactions: Inhibitors for the UDP-Glycosyltransferases (UGT) 1A1 and 1A9 may potentially increase the exposure of the pharmacologically active metabolite M1. Co-treatment with medicinal products increasing the upper gastro intestinal pH may lead to lower oral bioavailability. Antacids should be taken at least 2 hours before, or 1 hour after riociguat. Bosentan led to a decrease of riociguat steady-state plasma concentrations in PAH patients. Concomitant use of riociguat with strong CYP3A4 inducers may also lead to decreased riociguat plasma concentration. Refer to SmPC for complete information on drug-drug interactions.

Pregnancy and lactation: Riociguat is contraindicated during pregnancy. Animal studies have shown reproductive toxicity & placental transfer. Women of childbearing potential must use effective contraception. Monthly pregnancy tests are recommended. Riociguat should not be used during breastfeeding due to potential for serious adverse reactions in breast-fed infants.

Effects on ability to drive and use machines: Riociguat has moderate influence on the ability to drive and use machines. Dizziness has been reported and may affect ability to drive & use machines.

SIDE EFFECTS
"Refer to Summary of Product Characteristics for complete information on side-effects"

Serious adverse events: haemoptysis and pulmonary haemorrhage, including cases with fatal outcome. *Very common*: dizziness, headache, dyspepsia, diarrhoea, nausea, vomiting, peripheral oedema *Common:* gastroenteritis, anaemia, palpitations, hypotension, epistaxis, nasal congestion, gastritis, gastro-oesophageal reflux disease, dysphagia, gastrointestinal and abdominal pains, constipation, abdominal distension.

PACKAGE QUANTITIES AND BASIC NHS COST:
0.5, 1, 1.5, 2 or 2.5 mg x 42 tablets: £997.36;
2 or 2.5 mg x 84 tablets: £1994.72

Marketing Authorisation numbers:
UK (Northern Ireland): EU/1/13/907/001-020
Great Britain: PLGB 00010/0670-0674

Marketing Authorisation Holder:
UK (Northern Ireland):
Bayer AG, 51368 Leverkusen, Germany

Great Britain:
Bayer plc, 400 South Oak Way, Reading, RG2 6AD

Legal Category: POM

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