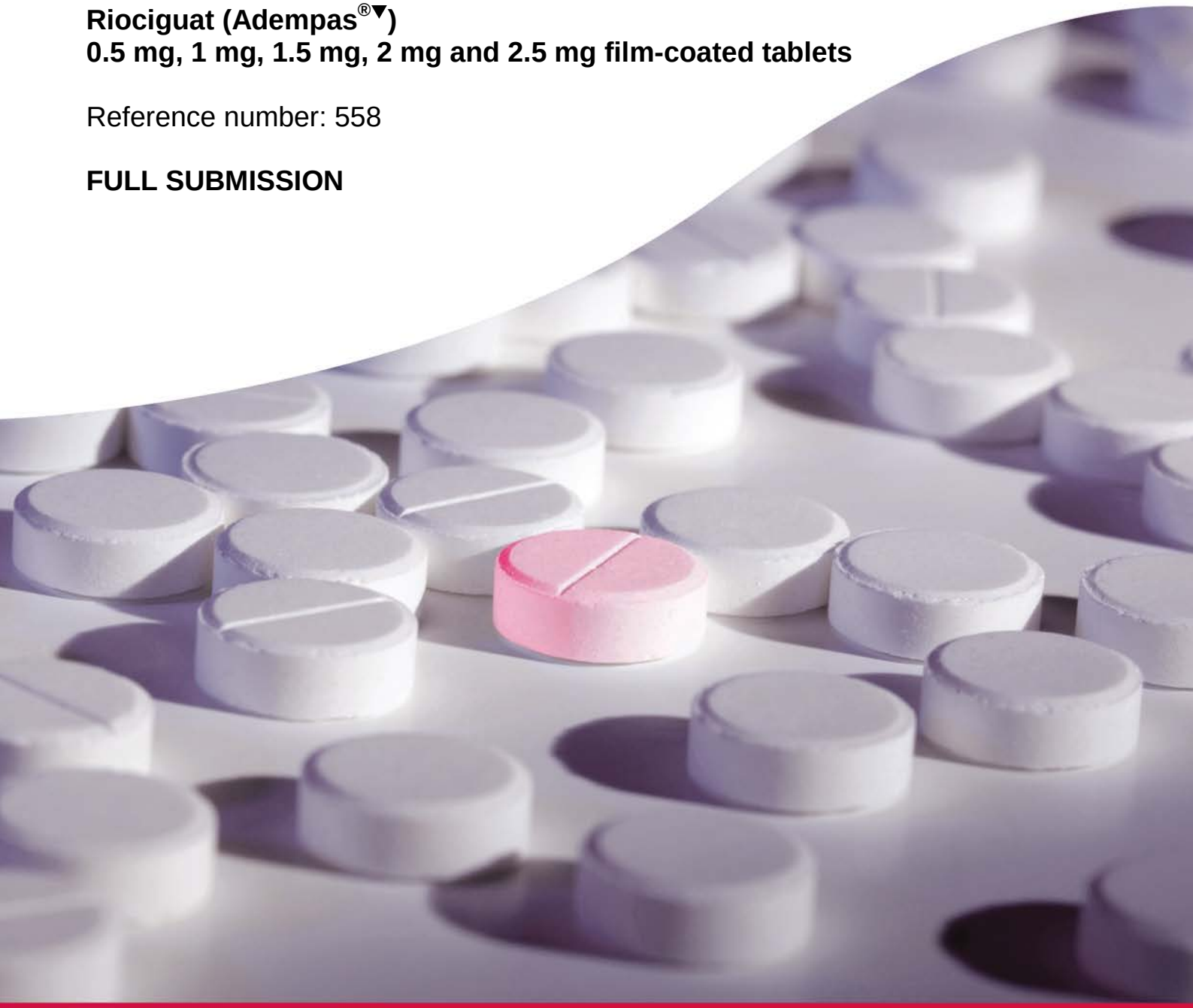
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

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

Reference number: 558

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Riociguat (Adempas®▼)
0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg film-coated tablets

This assessment report is based on evidence submitted by Bayer Healthcare Pharmaceuticals on 19 March 2015[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Riociguat (Adempas®▼) as monotherapy or in combination with endothelin receptor antagonists, for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO functional class II to III to improve exercise capacity. Refer to the Summary of Product Characteristics (SPC) for the full licensed indication[2–6].
Dosing	The recommended starting dose is 1 mg three times daily approximately six to eight hours apart for two weeks. Dose should be increased by 0.5 mg three times daily every two weeks to a maximum of 2.5 mg three times daily, if systolic blood pressure is ≥ 95 mmHg and the patient has no signs or symptoms of hypotension. The established individual dose should be maintained unless signs and symptoms of hypotension occur. Refer to the SPC for further information regarding dose titration and administration[2–6].
Marketing authorisation date	27 March 2014[2–6].

2.0 DECISION CONTEXT

2.1 Background

Pulmonary arterial hypertension (PAH) is a rare type of pulmonary hypertension, resulting from extensive remodelling of the pulmonary circulation, where blood vessels become increasingly constricted leading to increase in pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR)[1,7]. PAH is a chronic, debilitating disease characterised by breathlessness, fatigue, weakness, angina, syncope, and abdominal distension[8]. It is a progressive disease, and ultimately leads to right heart failure and death[7]. The lowest estimate of PAH incidence is 2.4 cases per million adult population per year. Recent data have confirmed that PAH prevalence is in the range of 15–50 patients per million population in Europe[8].

PAH remains a chronic disease without a cure[1,8]. Treatment aims to improve patients' symptomatic status and slow rate of clinical deterioration. Patients receive general cardiovascular therapies (e.g. calcium channel blockers, anticoagulants, diuretics) as best supportive care as well as treatments specifically licensed for PAH[1]. The PAH-specific treatment received depends on the severity of the disease as classified by World Health Organisation (WHO) functional class. Patients in WHO functional class II or III are managed with phosphodiesterase-5 inhibitors (PDE5i) or endothelin receptor antagonists (ERA)[1,7,8]. Prostanoids are predominantly used in patients who have the most severe disease (i.e. WHO functional class IV)[1,9].

Riociguat (Adempas®▼) is a novel stimulator of soluble guanylate cyclase (sGC), licensed in the UK for use in this population[1,7]. Riociguat has been granted orphan designation by the European Medicines Agency (EMA) for the treatment of PAH[7,10].

The All Wales Medicines Strategy Group (AWMSG) appraise medicines within the whole of its licensed indication; however, the applicant company have highlighted that the expected place in therapy for riociguat (Adempas®▼) is likely to be as an alternative treatment option to monotherapy with an ERA[1]. In Wales, ERAs are generally used in patients who are not appropriate for a PDE5i or in patients who have first failed treatment with a PDE5i[1,11].

The company is not requesting a position for riociguat in combination with other PAH-specific treatments (ERAs or prostanoids).

It should be noted that Riociguat (Adempas®▼) was also licensed on 27 March 2014 for the treatment of adult patients with WHO functional class II to III with inoperable chronic thromboembolic pulmonary hypertension (CTEPH); or persistent or recurrent CTEPH after surgical treatment to improve exercise capacity[2–6].

2.2 Comparators

The comparators included in the company submission were:

- Bosentan (Tracleer®)
- Ambrisentan (Volibris®)
- Macitentan (Opsumit®▼)

2.3 Guidance and related advice

- Galie N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension (2013)[9].
- Welsh Health Specialised Services Committee (WHSSC). Specialised services policy: drug therapy for pulmonary hypertension CP11 (2013)[11].
- Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology and the European Respiratory Society, endorsed by the International Society of Heart and Lung Transplantation (2009)[8].

AWMSG has previously issued recommendations for the use of ambrisentan (Volibris®)[12] and sildenafil (Revatio®)[13]. AWMSG has also issued Statements of Advice for the use of macitentan (Opsumit®▼)[14] and bosentan (Tracleer®)[15]. It should be noted that the WHSSC policy for pulmonary hypertension, clinical expert opinion and usage figures obtained by AWTTC demonstrate that these medicines are in use within NHS Wales for the indication under consideration.

AWMSG is concurrently appraising riociguat (Adempas®▼) for the treatment of adult patients with WHO functional class II to III with inoperable chronic thromboembolic pulmonary hypertension (CTEPH); or persistent or recurrent CTEPH after surgical treatment to improve exercise capacity[16].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included details of one pivotal phase III study (PATENT-1) and its long-term extension study (PATENT-2) to evaluate the efficacy and safety of oral riociguat in patients with PAH[1]. The company also conducted a systematic review and indirect treatment comparisons (ITCs) to examine the efficacy of riociguat compared to ERAs[1].

3.1 PATENT-1 study

PATENT-1 was a multicentre, randomised, double-blind, placebo-controlled study in 443 patients aged 18 to 80 years of age[1,17]. All patients were receiving best supportive care for PAH; i.e. oral anticoagulants, diuretics, digitalis or calcium channel blockers[1]. Patients were stratified according to whether they were treatment-naïve (not receiving PAH-specific treatment at baseline) or pre-treated (patients on stable dose of an ERA or prostanoid at baseline) and were randomised to receive riociguat or placebo in addition to their existing therapy[1,17,18].

After a pre-treatment phase, patients were titrated (over eight weeks) to between 1 mg and 2.5 mg three times a day based on an individual dose titration scheme with a starting dose of 1 mg[1,17,18]. Participants were randomised (4:2:1) to riociguat at a dose up to 2.5 mg (n = 254), placebo (n = 126) or to riociguat at a dose capped at 1.5 mg (n = 63). The latter, was included in the study for exploratory purposes to provide information about lower riociguat doses but was not included in the efficacy analyses and will therefore not be discussed further. During the 4-week study phase that followed, patients remained on their optimal dose of riociguat[1,17,18].

The primary endpoint was change from baseline to the end of week 12 in the distance walked in six minutes (6MWD)[1,17,18]. This demonstrated a statistically significant increase by a mean of 29.6 m in the riociguat groups (n= 254; treatment-naïve plus pre-treated) compared with a mean decrease of 5.6 m in the placebo group (n = 126); $p < 0.0001$)[1,17,18]. In prespecified subgroups of the ITT analysis set, the mean change in 6MWD was increased to a similar degree in both treatment-naïve patients (38.36 m; 95% confidence interval [CI]: 14.46 m to 62.26 m; n = 123) and pre-treated patients (35.65 m; 95% CI: 15.04 m to 56.26 m; n = 131) compared to placebo (treatment-naïve: n = 66; pre-treated: n = 60)[17]. In the subgroup analysis of subjects pre-treated with an ERA (n = 113), treatment response was smaller than the overall treatment effect for riociguat 1.0–2.5 mg, but was nevertheless greater than for placebo (25.89 m; 95% CI: 5.31 m to 46.48 m). A much larger treatment effect was observed in subjects pre-treated with a prostacyclin analogue (101.28 m; 95% CI: 26.53 m to 176.02 m). However, the applicant company acknowledge that the small sample sizes (riociguat 1.0–2.5 mg [n = 20], placebo [n = 7]) should be considered when interpreting this finding[17].

Statistically significant benefits favouring riociguat were also observed in the whole population for secondary outcomes of change from baseline in pulmonary vascular resistance (PVR), N-terminal pro-brain natriuretic peptide (NT-proBNP), and WHO functional class[1,17,18]. See Table 1 for results.

Table 1. Primary and secondary endpoint results from PATENT-1 study (ITT population)[1,17,18].

Endpoint	Riociguat			Placebo			Treatment comparison (LS mean difference [95% CI])
	N	Baseline	Change	N	Baseline	Change	
Mean (SD) 6-minute walking distance (m)* (whole study population)	254	361.4 (67.7)	29.6 (65.8)	126	367.8 (74.6)	−5.6 (85.5)	35.78 (20.06 to 51.51) p < 0.0001
Mean (SD) 6-minute walking distance (m)* (treatment-naïve subpopulation)	123	370 (66)	32 (74)	66	360 (80)	−6 (88)	38.36 (14.46 to 62.26) NR
Mean (SD) 6-minute walking distance (m)* (pre-treated subpopulation)	131	NR	NR	60	NR	NR	35.65 (15.04 to 56.26) NR
Mean (SD) PVR (dyn·second·cm^{-5}) † (whole study population)	232	791.0 (452.6)	−223.3 (260.1)	107	834.1 (476.7)	−8.9 (316.6)	−225.72 (−281.37 to −170.08) p < 0.0001
Mean (SD) NT-proBNP (picogram/ml)† (whole study population)	228	1026.7 (1799.2)	−197.9 (1721.3)	106	1228.1 (1774.9)	232.4 (1011.1)	−431.81 (−781.52 to −82.10) p = 0.0157
Change in WHO functional class† (whole study population)	254	5 patients (2%) in class I, 108 patients (43%) in class II, 140 patients (55%) in class III, 1 patient (0.4%) in class IV	53 patients (21%) moved to lower class (indicating improvement), 192 (76%) stayed in same class, 9 (4%) moved to higher class	125	4 patients (3%) in class I, 60 patients (48%) in class II, 58 patients (46%) in class III, 3 patients (2%) in class IV	18 patients (14%) moved to lower class (indicating improvement), 89 patients (71%) stayed in same class, 18 patients (14%) moved to higher class	NR p = 0.003

* Primary endpoint.
† Secondary endpoint.

CI: confidence interval; ITT: intention to treat; LS: least square; m: metres; N: number of patients; NR: not reported; NT-proBNP: N-terminal pro-brain natriuretic peptide; PVR: pulmonary vascular resistance; SD: standard deviation;

3.2 PATENT-2 study

At the end of the treatment period in the PATENT-1 study, eligible patients had the option to enter a two-year open-label extension safety and efficacy study (PATENT-2) where all patients (n = 396) were treated with an individual optimal dose of riociguat[1,18,19]. The study consisted of an eight–week double-blinded dose-adjustment phase to reach their optimum dose. Treatment was open-label thereafter[1,18,19].

A total of 98% of patients who completed PATENT-1 entered PATENT-2. Of these, 197 (50%) were receiving riociguat monotherapy (treatment-naïve subgroup of PATENT-1)[1,18,19]. A total of 141 patients (72%) were ongoing at two years; with 117 (83%) remaining on riociguat monotherapy. A total of six (4%) patients who had initially received combination therapy had transitioned to riociguat monotherapy at two years[1,18,19].

The primary endpoints were incidence of adverse events (AEs) and withdrawal rate[1] (see Section 3.4 for details). Secondary endpoints regarding efficacy were change in 6MWD and WHO functional class[1,19]. At two years, results demonstrated sustained clinical benefits in both treatment-naïve and pre-treated patients with PAH. Overall, mean 6MWD had increased from PATENT-1 baseline by 47 m (±85 m; n = 296) and WHO functional class had improved/stabilised/worsened compared with baseline in 33/58/9% of patients (n = 306)[1,19].

3.3 ITCs

The company conducted a systematic review and ITCs to examine the efficacy of riociguat monotherapy compared to bosentan, macitentan or ambrisentan[1]. No head to head studies were found; however, 10 studies were identified that could be used in ITCs. Of these 10 studies, one evaluated the efficacy and safety of riociguat (PATENT-1)[18], six evaluated bosentan[20–25], one evaluated macitentan[26] and two evaluated ambrisentan[27,28].

The studies used in the ITCs applied a variety of outcomes measures to assess the severity, progression and response to treatment[1]. A single significant result was shown in terms of riociguat patients being more likely to remain in the same WHO functional class compared to bosentan patients; however, no statistically significant difference between the two treatments was observed in terms of the risk of moving to a higher or lower WHO functional class. Overall, the ITCs are supportive of riociguat being of comparable efficacy and safety to bosentan. Results for efficacy and safety indicated no statistically significant difference between riociguat and macitentan or ambrisentan, with all CIs crossing zero[1].

3.4 Comparative safety

Evidence of the safety and tolerability of riociguat was provided as separate analyses of the pivotal phase III study (PATENT-1) and the long-term extension study (PATENT-2)[1].

In the PATENT-1 study, the overall frequency of treatment-emergent adverse events (TEAEs) was similar in the riociguat group (n = 227 [89%]) compared to the placebo group (n = 108 [86%])[1,17]. [Commercial in confidence information removed].

In the PATENT-2 study, the most frequent treatment-related TEAEs were dizziness (10%), dyspepsia (9%), and headache (8%)[1,19]. After two years, 10% of patients had withdrawn due to AEs, and 238 (60%) patients had experienced a serious AE (SAE). Of these, 39 (10%) patients experienced SAEs that were considered treatment-related; the most frequent being syncope (n = 13 [3%]). Three (1%) deaths were considered treatment-related (PAH, pulmonary haemorrhage, haemoptysis)[1].

The Committee for Medicinal Products for Human Use (CHMP) concluded that based on the current level of data the risk-benefit balance of riociguat is positive[7].

3.5 AWTTC critique

- In their submission the applicant company seeks a position for riociguat as a PAH-specific monotherapy for the treatment of adult patients with PAH of WHO functional class II or III. This would be as an alternative therapy to an ERA. However, the pivotal trials and ITCs were not conducted in patients for whom a PDE5i is either ineffective or not appropriate (where ERAs are currently positioned on the clinical pathway). The extent to which the trial outcomes would be reflected in clinical practice is therefore uncertain.
- In the absence of any direct comparative data, the applicant company conducted ITCs. Limitations of the ITC analyses acknowledged by the applicant included those caused by the small patient numbers and heterogeneity in study populations[1]. As a result, the conclusions drawn from the ITCs should be interpreted with caution in light of these limitations
- The applicant company claimed that the treatment-naïve subgroup in the PATENT-1 study provided the most relevant data for the efficacy of riociguat as a PAH-specific monotherapy[1]. Patients were excluded from this subgroup if they had received PDE5i; however, the company acknowledge that most patients following the standard treatment pathway for PAH would have first tried a PDE5i[1].
- In the PATENT-1 study, patients with unstable conditions were excluded. The applicant company acknowledge this as a limitation of the evidence base for riociguat since patients seen in clinical practice may be more unwell than those enrolled in the study[1].
- The choice of the 6MWD as the primary endpoint was in line with the relevant CHMP guideline[7,29]. However, the same guideline underscores the importance of investigating more clinically relevant endpoints such as time to clinical worsening. If the six minute walking test is investigated, an actively-controlled study design should have been used, also in line with the relevant guideline[7,29].
- CHMP highlighted that riociguat belongs to a new therapeutic group: sGC stimulators[7]. As such its safety profile is limited to data from the current application. The interaction with other therapies used and the disease characteristics may add complexity to the safety profile[7].
- The company claim that an advantage of riociguat over the currently available ERAs is that liver function and haemoglobin concentration is monitored routinely in patients being treated with ERAs. This is not a requirement of riociguat treatment[2–6].
- There are five different strengths of tablets. CHMP, however, have considered the preventative measures to avoid medication errors to be sufficient[7]. For example, each strength of tablet is coloured differently[30].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-minimisation analysis (CMA) of riociguat compared against the ERAs bosentan, ambrisentan and macitentan in the management of patients with WHO functional class II to III PAH[1]. The company has restricted its economic evidence to the use of riociguat as monotherapy in patients who are either ineligible for first-line treatment with a PDE5i such as sildenafil, or require second-line treatment with ERA after failure of PDE5i therapy.

In the absence of direct comparative data for riociguat and the comparators, pairwise Bucher adjusted ITCs have been conducted using data from treatment-naïve patients included in one riociguat (PATENT-1), six bosentan, two ambrisentan and one macitentan placebo-controlled trials identified in a systematic literature review. Based on these ITCs, the company reports there are no statistically or clinically significant differences between riociguat and the comparators across a range of key efficacy and safety endpoints, and therefore concludes that riociguat and the ERAs are therapeutically comparable[1].

Resource use included in the CMA relates to initiation of therapy and dose titration. Riociguat is assumed to require one hospital visit for initiation and three further visits for dose titration. In contrast, bosentan and ambrisentan are assumed to require one initiation visit and only one titration visit, and macitentan only a visit for initiation. Ongoing monitoring and AEs associated with treatment are assumed to be the same for each treatment. Riociguat acquisition costs include a confidential discount on its list price as part of a Wales Patient Access Scheme (WPAS).

A two year time horizon is assumed, and no discounting to net present value has been applied[1].

4.1.2 Results

Results of the CMA are presented in Table 2. [Commercial in confidence information removed].

Table 2. CMA results over a two-year time horizon[1].

Item	Riociguat	Bosentan	Ambrisentan	Macitentan
Year 1				
Acquisition cost	¶	£19,686.67	£19,686.64	£28,056.33
Initiation visit cost	£166.00	£166.00	£166.00	£166.00
Titration visit cost	£279.00	£93.00	£93.00	£0
Total	¶	**£19,945.67**	**£19,945.64**	**£28,222.33**
Year 2				
Acquisition cost (Total)	¶	**£19,686.67**	**£19,686.64**	**£28,056.33**
¶Commercial in confidence information removed				

Across a range of sensitivity analyses conducted around the data included in the adjusted ITCs, there were no statistically significant differences estimated for efficacy or safety outcomes. [Commercial in confidence information removed]. However, this does not account for the three additional hospital visits required for riociguat dose titration.

4.1.3 AWTTC critique

The company has presented a CMA of riociguat monotherapy compared against licensed ERAs in patients with PAH when a PDE5i is either ineffective or not appropriate. There is a lack of robust comparative data for riociguat and the comparators. The company's CMA therefore relies on limited evidence from ITCs of placebo-controlled trial data. These analyses are subject to several limitations due to small patient numbers, and heterogeneity in patient characteristics and trial durations. Further, as the trials were not conducted in patients for whom a PDE5i is either ineffective or not appropriate, the extent to which these data would reflect relative outcomes in the target patient population is uncertain. Based on these data, riociguat and the comparator ERAs are estimated by the company to have comparable efficacy and safety when assessed across a range of outcomes. [Commercial in confidence information removed].

Key strengths of the economic evidence include:

- In the absence of robust comparative data, the company has undertaken a systematic literature search to identify relevant trials with which to conduct adjusted ITCs. A range of outcomes were assessed from the available data to support the claim of comparable efficacy and safety.

Key limitations and uncertainties in the economic evidence include:

- The company has limited its economic evidence to a subset of the PAH licensed indication[2–6]. The analyses relate only to use of riociguat as monotherapy when a PDE5i is no longer effective or is not appropriate. Use of riociguat as either a first-line agent when a PDE5i is a treatment option, or in combination with other PAH agents, is not considered in the company's submission.
- The CMA framework assumes therapeutic equivalence in all domains of health outcomes. There is a lack of direct comparative data for riociguat and potential comparators and indirect comparative data are acknowledged by the company to be limited, being based on relatively small patient subgroups, with differing baseline characteristics, and who were treated for different durations. Resulting CIs around all indirect effect size estimates are large, and the extent to which these span clinically meaningful differences in outcomes is unclear.
- The riociguat and comparator trial data included in the adjusted ITCs were not conducted specifically in the target population of patients in whom PDE5i therapy is inappropriate or not effective. The extent to which these trial data would reflect outcomes in the proposed target population is unclear.
- [Commercial in confidence information removed].

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on Welsh data from the National Audit of Pulmonary Hypertension, 2013[31], the company estimates 82 patients received treatment for PAH in 2013. These data suggest that 19% of patients are currently treated with ERA monotherapy, equivalent to 16 patients potentially eligible for riociguat. The Audit data indicate a 6% increase in all pulmonary hypertension cases between 2012–2013, which is assumed by the company to persist for PAH in each of the next five years. A 25% uptake of riociguat in year one, rising to 50% in subsequent years is assumed.

Medicine acquisition costs for riociguat are based on the WPAS-price, and for comparator ERAs are assumed to be represented by the list price of bosentan, as the most commonly used ERA. Riociguat is assumed to require one hospital visit for initiation and three further titration visits, which are estimated to cost £445 in total per

patient. In contrast, the ERAs (based on bosentan) are assumed to require one initiation visit and only one titration visit, at a total cost of £259 per patient.

5.1.2 Results

Based on the confidential WPAS-price of riociguat, the net budget impact of the introduction of riociguat in NHS Wales is presented in Table 3. [Commercial in confidence information removed].

Table 3. Company estimates of net cost implications associated with use of riociguat for the treatment of PAH.

	Year 1	Year 2	Year 3	Year 4	Year 5
Current situation (riociguat not available)					
Number of patients on ERA monotherapy	16	17	18	19	20
Annual cost (per patient = £19,945.67)	£319,130.72	£339,076.39	£359,022.06	£378,967.73	£398,913.40
Future (riociguat available)					
Number of patients on ERA monotherapy	12	9	9	10	10
Annual cost (per patient = £19,945.67)	£239,348.04	£169,538.20	£179,511.03	£189,483.87	£199,456.70
Number of patients on riociguat monotherapy	4	8.5	9	9.5	10
Annual cost (per patient = ¶)	¶	¶	¶	¶	¶
Total	¶	¶	¶	¶	¶
Net Budget Impact (future - current)	¶	¶	¶	¶	¶

ERA: endothelin receptor antagonist; PAH: pulmonary arterial hypertension.
¶Commercial in confidence information removed.

No alternative scenarios or sensitivity analyses have been provided.

5.1.3 AWTTC critique

- The company has adopted a pragmatic approach to estimate the number of patients with PAH eligible for treatment with riociguat.
- ERA costs are assumed to be those of bosentan, as this is the most commonly used ERA. Alternative comparator costs have not been explored.
- The additional hospital visits required for riociguat dose titration are included in the budget impact estimates as additional financial costs in each year; however, in the context of fixed capacity, these may not reflect the opportunity costs in practice of the associated additional resource use.
- ERA monotherapy is the main comparator considered in the budget impact analyses. The company's budget impact analysis relates only to use of riociguat in those patients who have failed on or are unable to take PDE5i, and only when used as monotherapy.

5.2 Comparative unit costs

Example annual maintenance costs (excluding titration) of riociguat and other treatments licensed for use in PAH are included for reference in Table 4, based on British National Formulary list prices (exclusive of VAT)[32].

Table 4. Example comparative costs of riociguat and other PAH treatments.

Medicine	Example regimen	Annual costs*
Riociguat (Adempas®▼) tablets	1.5 mg to 2.5 mg three times per day	£26,003
Bosentan (Tracleer®) tablets	62.5 mg to 125 mg twice daily	£19,687
Ambrisentan (Volibris®) tablets	5 mg once daily	£19,687
Iloprost (Ventavis®) nebuliser solution	2.5 micrograms to 5.0 micrograms six to nine times daily	£7,304 to £21,911
Macitentan (Opsumit®▼) tablets	10 mg once daily	£28,056
Sildenafil (Revatio®) tablets	20 mg three times daily	£5,430
Tadalafil (Adcirca®) tablets	40 mg once daily	£6,403
This table does not imply therapeutic equivalence of medicines or doses. See relevant Summaries of Product Characteristics for full dosing details[2–6,33–39]. *Costs based on British National Formulary list prices, as of April 2015. A confidential discount on the list price of riociguat is available to NHS Wales via a Wales Patient Access Scheme.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, riociguat (Adempas®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipate that riociguat (Adempas®▼) may be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months[1].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 16 April 2015
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

Riociguat has been granted orphan status for the treatment of PAH and also CTEPH[10]. Based on data from the National Audit of Pulmonary Hypertension, 2013, the company estimates there are 82 patients treated for PAH in Wales[31].

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