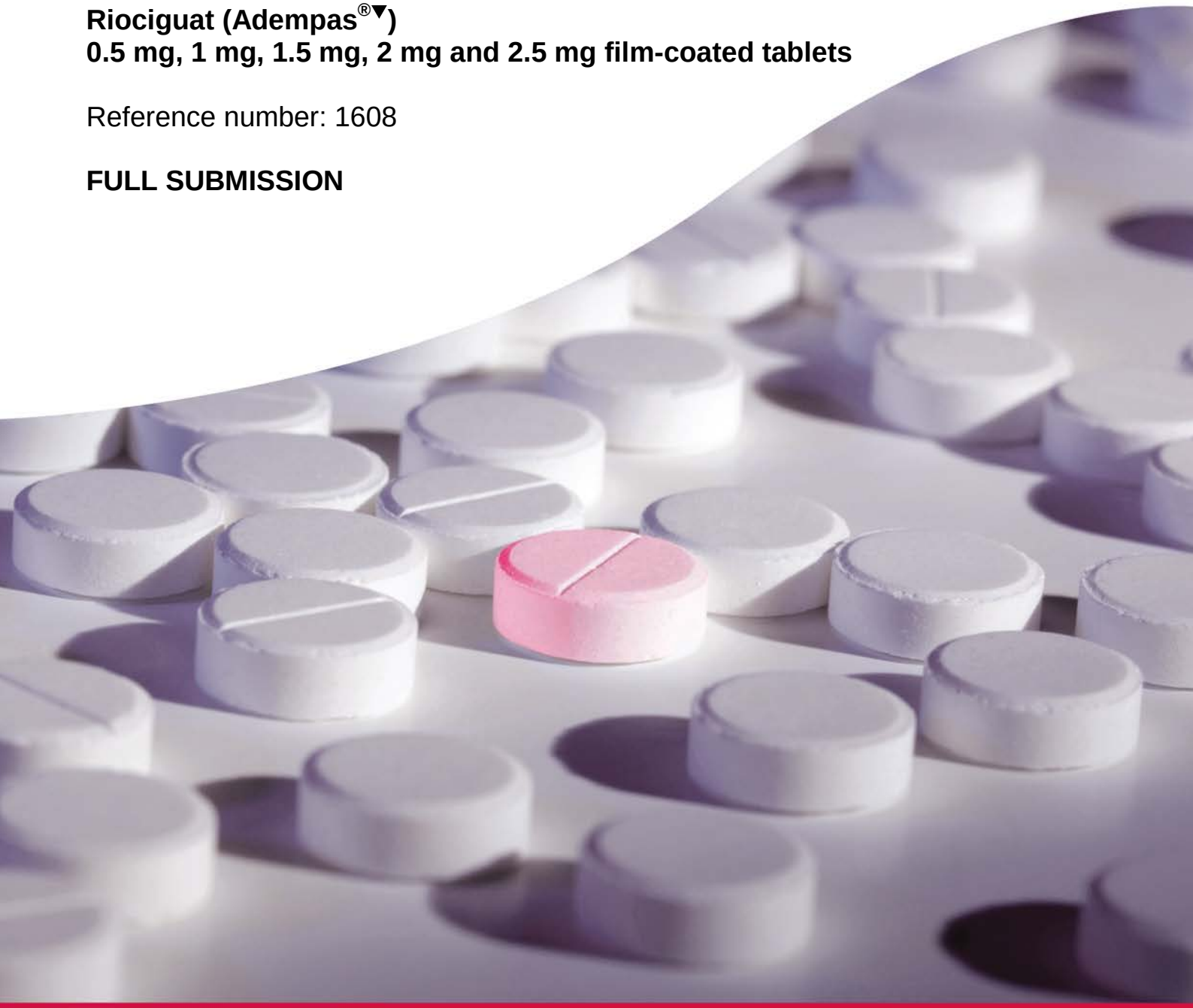
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

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: 1608

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

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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 13 March 2015[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	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. 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 (also licensed 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, on 27 March 2014)[2–6].

2.0 DECISION CONTEXT

2.1 Background

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare type of pulmonary hypertension (PH), most often resulting from obstruction of the pulmonary vascular bed by non-resolving thromboemboli[1,7]. CTEPH is a chronic, debilitating disease characterised by dyspnoea, fatigue, chest pain, dizziness, peripheral oedema, coughing, haemoptysis, and, in advanced disease, fainting and syncope[1,7]. The incidence of CTEPH is not known[1,7], but recent studies suggest that 1% to 3.8% of patients develop the condition within two years of acute pulmonary embolism[7]. Without intervention, the prognosis of patients with CTEPH is poor and depends on the haemodynamic severity of PH[1,7].

Treatment for patients with CTEPH should include life-long anticoagulation[8]. The only potentially curative treatment is surgical removal of the obstructive material by pulmonary endarterectomy (PEA)[7,8]. However, a substantial percentage of patients with CTEPH are not operable, and 10% to 15% of operated patients suffer from persistent PH[7]. Pulmonary arterial hypertension (PAH)-specific medicines, including endothelin receptor antagonists (ERA: e.g. bosentan [Tracleer®]) and phosphodiesterase-5 (PDE5) inhibitors, are frequently used off-label in selected patients with CTEPH despite

there being no compelling evidence to support this approach[1,7,8]. Bilateral lung transplantation is an option for advanced cases that are not suited for PEA[8].

There are currently no approved medicines for patients with World Health Organisation (WHO) functional class II to III with inoperable CTEPH or persistent or recurrent CTEPH following surgical treatment[1,7,8]. 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, including CTEPH[7,9].

The All Wales Medicines Strategy Group (AWMSG) appraise medicines within the whole of its licensed indication; however, the company have highlighted that the expected place in therapy for riociguat (Adempas®▼) is likely to be where a PDE5 inhibitor is considered inappropriate, not tolerated, or ineffective, i.e. where ERAs are currently prescribed[1].

2.2 Comparator

The company highlight that there are no approved pharmaceutical agents in Europe that directly target CTEPH[1]. Bosentan (Tracleer®) and sildenafil (Revatio®) however, are included in the indirect treatment comparison (ITC) analyses, despite being off-label products lacking demonstrated efficacy in the treatment of CTEPH.

2.3 Guidance and related advice

- Welsh Health Specialised Services Committee (WHSSC). Specialised services policy: drug therapy for pulmonary hypertension CP11 (2013)[10].
- 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 is concurrently appraising riociguat (Adempas®▼) as monotherapy or in combination with endothelin receptor antagonists, for the treatment of adult patients with PAH with WHO functional class II to III to improve exercise capacity[11].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included details of one pivotal phase III study (CHEST-1) and interim data analyses from an ongoing long-term extension study (CHEST-2) to evaluate the efficacy and safety of oral riociguat in patients with CTEPH[1]. The company also conducted a systematic review and ITC to examine the efficacy of PAH-specific medicines used off-label for the treatment of CTEPH[1].

3.1 CHEST-1 study

CHEST-1 was a multicentre, randomised, double-blind, placebo-controlled study in 261 patients aged 18 to 80 years of age with inoperable CTEPH or persistent or recurrent pulmonary hypertension after PEA[1,12,13]. Most patients were in WHO functional class II or III (31% and 64%, respectively), and more patients had inoperable CTEPH (72%) than postoperative persistent or recurrent pulmonary hypertension (28%)[1,13]. Eligible patients were to be therapy-naïve with respect to PAH-specific medications; however, if patients pre-treated with PAH-specific medication had suffered from unacceptable adverse reactions and/or missing benefit, they were considered for study inclusion[1,12]. Patients, however, were excluded if they had received PAH-specific medication within the three months before study entry[1,12,13].

The study consisted of a four–week pre-treatment phase followed by an eight–week titration phase, then an eight–week main study phase[1,12,13]. After the pre-treatment phase patients were randomised 2:1 to the riociguat group (n = 180) or placebo group (n = 90)[1,12,13]. Patients were titrated 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[1,12]. During the study phase, patients remained on their optimal dose of riociguat[1,12].

The primary endpoint was change from baseline in the distance walked in six minutes (6MWD) after 16 weeks[1,12,13]. This demonstrated a statistically significant increase by a mean of 39 m in the riociguat group compared with a mean decrease of 6 m in the placebo group ($p < 0.0001$)[1,12,13]. [Commercial in confidence information removed]. Statistically significant benefits favouring riociguat were also observed for secondary outcomes of change from baseline in pulmonary vascular resistance (PVR), N-terminal pro-brain natriuretic peptide (NT-proBNP), and WHO functional class[1,12]. See Table 1 for results.

Table 1. Primary and secondary endpoint results from CHEST-1 study (ITT population)[1,12].

Endpoint	Riociguat			Placebo			Treatment comparison (LS mean difference [95% CI])
	N	Baseline	Change	N	Baseline	Change	
Mean (SD) 6-minute walking distance (m)[†]	173	342.3 (81.9)	38.9 (79.3)	88	356.0 (74.7)	−5.5 (84.3)	45.69 (24.74 to 66.63) p < 0.0001
Mean (SD) PVR (dyn*second*cm^{-5})[§]	151	790.7 (431.6)	−225.7 (247.5)	82	779.3 (400.9)	23.1 (273.5)	−246.43 (−303.33 to −189.53) p < 0.0001
Mean (SD) NT-proBNP (picogram/ml)[§]	150	1508.3 (2337.8)	−290.7 (1716.9)	73	1705.8 (2567.2)	76.4 (1446.6)	−443.99 (−842.95 to −45.03) p = 0.0293
Change in WHO functional class[§]	173	3 patients (2%) in class I; 55 patients (32%) in class II; 107 patients (62%) in class III	57 patients (33%) moved to lower class (indicating improvement); 107 patients (62%) stayed in same class; 9 patients (5%) moved to higher class	87	0 patients in class I; 25 patients (29%) in class II; 60 patients (69%) in class III; 2 patients (2%) in class IV	13 patients (15%) moved to lower class (indicating improvement); 68 patients (78%) stayed in same class; 6 patients (7%) moved to higher class	NR p = 0.0026

[†]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 CHEST-2 study

At the end of the treatment period in the CHEST-1 study, eligible patients had the option to enter a long-term open-label extension safety study (CHEST-2) where all patients were treated with an individual optimal dose of riociguat[1]. A total of 237 patients (91%) who completed CHEST-1 entered CHEST-2. The study consisted of an eight–week blinded titration phase, where patients in the riociguat arm continued on their optimum dose and patients from the placebo arm were titrated to their optimum dose of riociguat (up to 2.5 mg three times a day). The study continued as an open-label single arm study and is currently ongoing[1].

The primary endpoints are incidence of adverse events (AEs) and withdrawal rate (see Comparative Safety section for details). Secondary endpoints regarding efficacy are change in 6MWD and WHO functional class[1]. Interim results (cut-off date May 2012) provided by the company support the findings of the CHEST-1 study, demonstrating sustained clinical benefits in patients with CTEPH. [Commercial in confidence information removed]

The company report that at March 2013, 211 (89%) patients were still continuing in the study and a further interim analysis of the 179 (76%) who had received one year or more of treatment with riociguat was undertaken at this time[1]. Results from this cohort of patients show that after 12 months in CHEST-2, the secondary outcome of mean 6MWD had increased by 51 m from the CHEST-1 baseline (n = 172), and WHO functional class had improved in 46% of patients, was stable in 49% and worse in 3% of patients compared with the CHEST-1 baseline (n = 178)[1].

3.3 Systematic review and ITC

The company conducted a systematic review and ITC to examine the efficacy of PAH-specific medicines used off-label for the treatment of CTEPH[1]. The review identified two placebo controlled studies[14,15] that could be used in an ITC which, combined with data from the CHEST-1 study[12] (unpublished at the time of the review and ITC), allowed for the comparison of riociguat to sildenafil and bosentan in the treatment of patients with inoperable CTEPH or persistent/recurrent pulmonary hypertension after surgical treatment[1].

In the primary end point (change in 6MWD), riociguat showed significant improvement over bosentan of 42.2 m gain (95% CI: 9.8 to 74.8; p = 0.01). Riociguat also showed levels of benefit against sildenafil of 26.9 m (95% CI: −16.1 to 70.2); however, this was not statistically significant (p = 0.22)[1].

3.4 Comparative safety

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

In the CHEST-1 study, treatment-emergent adverse events (TEAEs) were reported in 159 (91.9%) patients in the riociguat treatment group and 76 (86.4%) patients in the placebo group[1,12]. The overall frequency of medicine-related TEAEs was higher in the riociguat group than in the placebo group (103 [59.5%] patients versus 36 [40.9%] patients). Medicine-related TEAEs reported at least 5% more frequently in the riociguat group than in the placebo group were headache (15.6% versus 8.0%), dizziness (15.0% versus 3.4%), dyspepsia (12.1% versus 6.8%), and hypotension (8.1% versus 0%). Medicine-related serious TEAEs were reported for 6 (3.5%) patients in the riociguat group and 1 (1.1%) patient in the placebo group[12]. Syncope was reported as a medicine-related serious TEAE for 3 (1.7%) patients in the riociguat group and 1 (1.1%) patient in the placebo group. All other medicine-related serious TEAEs each occurred only in 1 patient of a treatment group. TEAEs leading to discontinuation of study medication were considered medicine-related in one patient[12].

In the CHEST-2 study, TEAEs were reported in 173 (89%) patients, of which 83 (43%) were considered medicine-related[1,16]. The most frequent medicine-related TEAEs (> 5%) were dizziness (riociguat: 9%; placebo: 8%), dyspepsia (riociguat: 7%; placebo: 8%), and hypotension (riociguat: 5%; placebo: 8%). Serious TEAEs were reported by 59 (30%) patients, of which eight (4%) were considered medicine-related[1,16].

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 suggest riociguat should be considered as an alternative treatment option to ERAs in adult patients with inoperable CTEPH of WHO functional class II to III, or persistent or recurrent CTEPH after surgical treatment[1]. Not all study participants, however, were patients in whom treatment with a PDE5 inhibitor was considered inappropriate, not tolerated, or ineffective. There is therefore no direct or indirect evidence relating specifically to the company's proposed position.
- As of April 2015, riociguat is the only UK licensed product for the treatment of CTEPH.
- In the absence of any direct comparative data, the applicant company conducted an ITC. Limitations of the ITC analysis acknowledged by the applicant company were those caused by the small number of studies included, differences in treatment comparisons, small sample size in the sildenafil study, possible differences in what constituted standard therapy and concomitant treatments[1]. As a result, the conclusions drawn from the ITC should be interpreted with caution in light of these limitations.
- The choice of the 6MWD as the primary endpoint was in line with the relevant CHMP guideline[7,17]. 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[7,17].
- CHMP highlight that the efficacy was limited in patients with WHO functional class II[7]. However, CHMP accept that it is difficult to show robust improvements in such patients as the margin in improvement is limited. There was also a substantial improvement in the placebo group, limiting the difference. Patients can shift between functional class II and III, and CHMP conclude that it does not appear practical to specifically exclude functional class II patients from the indication as it would probably only lead to the off-label use of the medicine in this subgroup[7].
- 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].
- [Commercial in confidence information removed]
- Unlike patients treated with currently available ERAs[18], monitoring of liver function and haemoglobin levels is not routinely required for those receiving a maintenance dose of riociguat[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[19].

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 bosentan as monotherapy in the treatment of WHO functional class II to III inoperable CTEPH or persistent or recurrent CTEPH after surgical treatment, to improve exercise capacity[1]. The company has restricted its economic evidence to the use of riociguat in patients who are either ineligible for first-line treatment with a PDE5 inhibitor such as sildenafil, or require second-line treatment after failure of PDE5 inhibitor therapy. A supplementary cost-utility analysis (CUA) of the same comparison has also been provided.

In the absence of direct comparative data, an adjusted ITC has been conducted using data from one riociguat (CHEST-1) and one bosentan (BENEFiT) placebo-controlled trial identified in a systematic literature review. This ITC estimated riociguat to be statistically superior to bosentan for the primary efficacy endpoint of change in 6MWD from baseline. A statistically significantly lower rate of hepatic dysfunction was also noted in favour of riociguat, but no statistically significant differences in any other efficacy or safety endpoints were observed (see Section 3). On this basis, riociguat was assumed to be at least as effective and safe as bosentan.

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 titration visits. In contrast, bosentan is assumed to require one initiation visit and only one titration visit. Ongoing monitoring and AEs associated with treatment are conservatively 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.

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	Difference
Year 1			
Acquisition cost	¶	£19,686.67	¶
Initiation visit cost	£166.00	£166.00	£0.00
Titration visit cost	£279.00	£93.00	£186.00
Total	¶	**£19,945.67**	¶
Year 2			
Acquisition cost (Total)	¶	**£19,686.67**	¶
¶Commercial in confidence information removed			

In the supplementary CUA, riociguat dominated bosentan (i.e. riociguat was estimated to be overall less costly and to provide more quality-adjusted life years [QALYs] than bosentan) over a lifetime (40 year) horizon of analysis[1]. Key drivers of the results are the improvement in WHO functional class and avoidance of higher cost escalation therapy with riociguat compared with bosentan, as modelled. Riociguat remained the

preferred treatment in the majority of a wide range of sensitivity and scenario analyses exploring key parameter values.

4.1.3 AWTTC critique

The company presented a primary CMA and a supplementary full CUA of riociguat compared against bosentan, both as monotherapy, in patients with CTEPH when a PDE5 inhibitor is either ineffective or not appropriate[1]. There is a lack of robust comparative data for riociguat and bosentan, and the company's analyses therefore rely on ITCs of single trials, which are subject to limitations. Further, as the trials were not conducted in patients for whom a PDE5 inhibitor is either ineffective or not appropriate, the extent to which these data would reflect relative outcomes in the target patient population is uncertain. However, these appear to be the best available data and, based on these, riociguat is estimated to be potentially more effective than bosentan in terms of improvements in 6MWD. [Commercial in confidence information removed].

The company suggests that riociguat should be considered under the AWMSG policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases (see Section 6.5).

Key strengths of the economic evidence include:

- The company selected bosentan as the most relevant comparator in the target population in line with the WHSSC pulmonary hypertension commissioning policy, which recommends first-line treatment should be with sildenafil or, when sildenafil is contraindicated or has proven not to have been of benefit after a trial period of three months, treatment should be with bosentan[10].
- There are limited efficacy data for riociguat and any potential comparators in the treatment of this rare condition. 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 efficacy and safety outcomes were considered in the ITC analyses.
- The company has provided a pragmatic CMA supplemented with a full CUA in support of its economic case for riociguat.

Key limitations and uncertainties in the economic evidence include:

- The company has limited its economic evidence to a subset of the CTEPH licensed indication[2–6].
- The primary analysis is a CMA, which assumes therapeutic equivalence in all domains of health outcomes. There is a lack of direct comparative data for riociguat and potential comparators. Therefore, adjusted ITCs using data from single, relatively short-term trials have been conducted, which are subject to limitations. Credible intervals around all indirect effect size estimates are large.
- The trial data included in the adjusted ITCs were not conducted specifically in the target population of patients in whom PDE5 inhibitor 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].
- The supplementary CUA uses relative treatment effect estimates derived from the ITCs, and is subject to the same limitations of these data as above.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on data from the UK National Audit of Pulmonary Hypertension, 2013, the prevalence of CTEPH in Wales is estimated to be 17.4 cases per million population[20]. Of all PH cases, 76.2% are in WHO functional class III and 3.8% class II. An international prospective registry study found that 37% of patients are inoperable, and of those who do receive surgical treatment, 17% have recurrent/persistent disease[21]. Applied to the population of Wales, the number of people meeting the licensed indication for riociguat is estimated to be 21. The company assumes this number will remain constant over the next five years and all will currently receive treatment[1].

The company reports the National Audit to have found 14.5% of WHO FC II patients and 23.1% of FC III patients receive bosentan[20]. Given that 3.8% of patients are WHO FC II and 76.2% are WHO FC III, of the 21 eligible patients, five are estimated to be currently prescribed bosentan for treatment of CTEPH. The company assumes that, following the introduction of riociguat, 50% of patients who would have previously received bosentan will instead receive riociguat[1].

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, bosentan is assumed to require one initiation visit and only one titration visit, at a total cost of £259.

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 CTEPH.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	5	5	5	5	5
Uptake (%)	50%	50%	50%	50%	50%
Treated patients	3	3	3	3	3
Net costs					
Treatment therapy	¶	¶	¶	¶	¶
Initiation and Titration	£558	£558	£558	£558	£558
Overall net cost	¶	¶	¶	¶	¶
¶Commercial in confidence information removed					

The company notes that the greatest area of uncertainty in its budget impact estimates concerns the number of eligible patients. As use of riociguat instead of bosentan induces cost-savings, the company considers this area of uncertainty to be of little consequence.

5.1.3 AWTTC critique

- As there is a lack of data on the specific treatment received by patients with CTEPH, the company has adopted a pragmatic approach to estimate the number of patients eligible for treatment with riociguat.
- 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.
- Bosentan is the only comparator considered in the budget impact analysis (and in the CMA in Section 4). The company has requested appraisal of riociguat only in those patients who have failed on or are unable to take PDE5 inhibitors, for whom bosentan monotherapy would otherwise be the routine line of therapy.

5.2 Comparative unit costs

Riociguat is the only agent licensed specifically for the treatment of CTEPH. Example annual maintenance costs (excluding titration) of other PH treatments that may be used (off-label) in practice in the treatment of CTEPH are included for reference in Table 4, based on British National Formulary list prices (exclusive of VAT)[22].

Table 4. Example comparative costs of riociguat and other PH treatments used for CTEPH.

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 (inhalation)	£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[2–6,18,23–27]. *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 highlighted one ongoing study that is likely to be available within 6–12 months: CHEST-2 study[1]. See section 3.2 for details.

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

The applicant company suggests that the use of riociguat in the given population meets the criteria for ultra-orphan status. The AWMSG policy defines an ultra-orphan medicine as a medicine that has been granted European Medicines Agency (EMA) designated orphan status and is used to treat a condition with a prevalence of 1 in 50,000 or less in the UK (or 60 patients in Wales). The definition applies to the full population of the licensed indication[28].

Riociguat has been granted orphan status for the treatment of PAH and CTEPH[9]. Based on data from the National Audit of Pulmonary Hypertension, 2013, the company reports the prevalence of CTEPH in Wales as 17.4 cases per million population[20], which is approximately equivalent to 54 patients in Wales. As riociguat is licensed only for use in those with WHO functional class II and III with inoperable CTEPH, or persistent or recurrent CTEPH after surgical treatment[2–6], the number of patients meeting the CTEPH licensed indication would be lower than this. The full population of the licensed indication for riociguat includes patients with WHO functional class II and III PAH. The company report that there are 82 patients treated for PAH in Wales. AWTTC does not consider riociguat to be eligible as an ultra-orphan medicine due to the full population of the licensed indication exceeding the 1 in 50,000 or less in the UK (or 60 patients in Wales) threshold.

Should NMG/AWMSG consider riociguat eligible to be considered as an ultra-orphan medicine, they will take broader considerations into account when appraising ultra-orphan medicines than those for orphan medicines, or for other medicines (see Table 5).

Table 5. Evidence considered by NMG/AWMSG.

NMG/AWMSG Considerations	AWTTC Comments
The degree of severity of the disease as presently managed, in terms of survival and quality of life impacts on patients and their carers.	CTEPH is a chronically debilitating and life-threatening condition[9].
Whether the medicine can reverse or cure, rather than stabilise the condition.	Based on data from the CHEST-1 study, riociguat was able to improve WHO functional class in a proportion of patients compared with placebo. In adjusted ITCs, riociguat was numerically but not statistically superior to bosentan in improving WHO functional class[1].
The innovative nature of the medicine.	There are no other treatments specifically licensed for use in CTEPH; current treatment includes off-label use of other agents that are licensed for PAH. Available indirect comparative data suggest riociguat is statistically and clinically superior to bosentan in its efficacy on exercise capacity (measured by 6MWD)[1]. [Commercial in confidence information removed].
Whether medicine addresses an unmet need.	Riociguat is the only treatment for recurrent, persistent or inoperable CTEPH that has met its primary endpoint in clinical trials. Furthermore, the applicant company claim that no other treatment has been able to show any clinical advantages relating to a patients capacity to exercise.
Added value to the patient which may not be captured in the QALY.	As well as some patients improving WHO functional class, the CHEST-1 trial showed an improvement in a range of clinical measures used to assess exercise capacity and disease severity. The applicant company suggest that the significant improvement in exercise capacity, and the improvement and stabilisation of patients' functional class over a long period of time is of significant advantage to patients and their families/ carers. The company claim that patients are able to experience more comfort, and are more able to easily perform simple daily activities, such as doing their own shopping, with much greater freedom.
6MWD: six minute walking distance; CUA: cost-utility analysis; PAH: pulmonary arterial hypertension; QALY: quality-adjusted life-year	

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