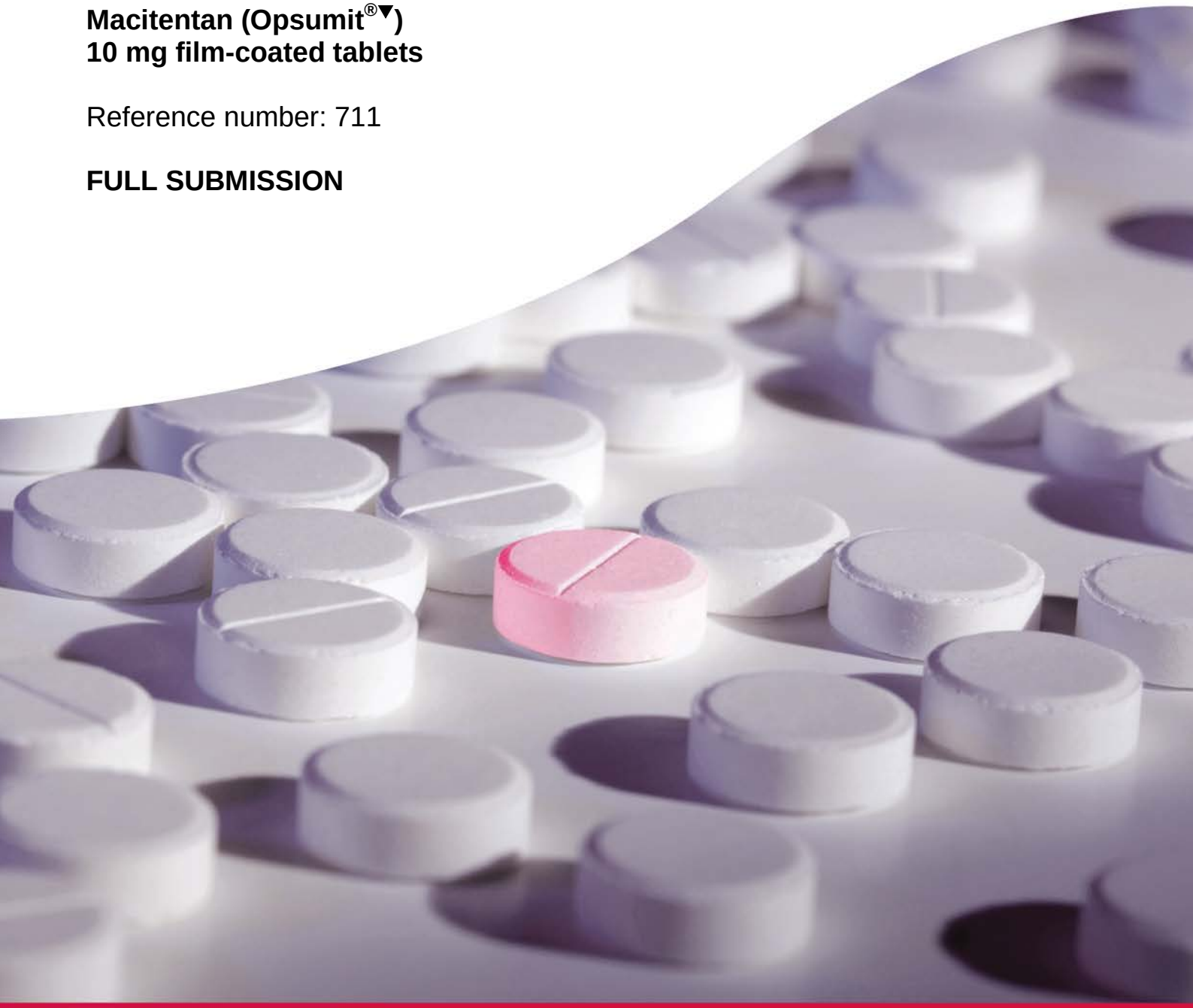
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Macitentan (Opsumit®▼)
10 mg film-coated tablets

Reference number: 711

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.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Macitentan (Opsumit®▼) 10 mg film-coated tablets. Reference number: 711. November 2015.

AWMSG Secretariat Assessment Report
Macitentan (Opsumit®▼) 10 mg film-coated tablets

This assessment report is based on evidence submitted by Actelion Pharmaceuticals UK Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Macitentan (Opsumit®▼) as monotherapy or in combination, for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III[2].
Dosing	10 mg to be taken orally once daily, with or without food, at about the same time of day[2].
Marketing authorisation date	20 December 2013[2].

2.0 DECISION CONTEXT

2.1 Background

Pulmonary arterial hypertension (PAH) is a rare, progressive disease of the small pulmonary arteries that is characterised by vascular proliferation and remodelling, resulting in increased pulmonary artery pressure and pulmonary vascular resistance and, ultimately, right ventricular heart failure and death[1,3]. PAH is a debilitating disease with symptoms of breathlessness, fatigue, weakness, angina, syncope, and abdominal distension[4]. Based on Welsh data from the National Audit of Pulmonary Hypertension, 2013, the applicant company have estimated a prevalence of 148 patients with PAH in Wales[1,5].

PAH remains a chronic disease without a cure[1,3,4]. Current treatment leads to improvement in patients' symptomatic status and a slower rate of clinical deterioration[4]. Patients receive general cardiovascular therapies (e.g. calcium channel blockers, anticoagulants, diuretics) as best supportive care as well as treatments specifically licensed for PAH. The PAH-specific treatment received depends on the severity of the disease as classified by World Health Organisation (WHO) functional class (FC). Patients in WHO FC II or III are managed mainly with phosphodiesterase-5 inhibitors (PDE5i) or endothelin (ET) receptor antagonists (ERA)[4,6]. Intravenous prostanoids are predominantly used in patients who have the most severe disease (i.e. WHO FC IV)[6,7]. 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[8].

Macitentan (Opsumit®▼) is an active potent ERA, active on both ET_A and ET_B receptors, and is licensed in the UK for use in the indicated population[1–3]. Macitentan has been granted orphan designation by the European Medicines Agency (EMA) for the treatment of PAH[9].

2.2 Comparators

The comparators included in the company submission were:

- Ambrisentan (Volibris®)
- Bosentan (Tracleer®)

2.3 Guidance and related advice

- NHS England. Clinical Commissioning Policy: national policy for targeted therapies for the treatment of pulmonary hypertension in adults (2014)[6].
- Galie N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension (2013)[7].
- Welsh Health Specialised Services Committee (WHSSC). Specialised services policy: drug therapy for pulmonary hypertension CP11 (2013)[8].
- 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)[4].

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of ambrisentan (Volibris®)[10], sildenafil (Revatio®)[11,12] and riociguat (Adempas®▼)[13]. AWMSG has also issued a Statement of Advice for the use of bosentan (Tracleer®)[14]. It should be noted that the WHSSC policy for pulmonary hypertension, clinical expert opinion and usage figures obtained by AWTTC demonstrate that bosentan (Tracleer®) is in use within NHS Wales for the indication under consideration.

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

To evaluate the long-term efficacy and safety of macitentan in patients with symptomatic PAH, the company submission included details of one phase III study (SERAPHIN)[1]. The company also conducted a systematic review and indirect treatment comparisons (ITCs) to examine the short-term efficacy of macitentan[1].

3.1 SERAPHIN study

SERAPHIN was a multicentre, double-bind, placebo-controlled, parallel-group, outcome study in 742 patients with PAH aged 12 years old and over[1,3,15]. This was an event-driven study, the duration of the study being dependent upon the occurrence of a pre-specified number of events.

The primary composite endpoint was the time from the initiation of treatment to the first event related to PAH (worsening of PAH, initiation of treatment with intravenous or subcutaneous prostanoids, lung transplantation, or atrial septostomy) or death from any cause up to the end of treatment[1–3,15]. Patients could discontinue at any time following randomisation, therefore the end of treatment period (EOT) was the date of discontinuation from double-blind treatment and the end of study (EOS) date occurred when the target of 285 morbidity-or-mortality events was reached.

Patients were randomised 1:1:1 to receive placebo, macitentan 3 mg, or macitentan 10 mg, once daily. Marketing authorisation was sought only for the 10 mg dose[1]: therefore, results for the macitentan 3 mg group are not reported here. Patients were either naive to PAH-specific treatment (placebo: 38.2%; macitentan: 36.4%) or were receiving concomitant treatment (placebo: 61.8%; macitentan: 63.6%)[15]: including oral PDE5i, oral or inhaled prostanoids, calcium channel blockers or L-arginine, provided that the dose had been stable for at least three months prior to randomisation[1,3,15]. Sildenafil was the most common PAH therapy[3].

The mean treatment duration was 85.3 weeks and 103.9 weeks for the patients receiving placebo and macitentan 10 mg, respectively[2,15]. Treatment with macitentan demonstrated a significant 45% reduction in the risk of morbidity and mortality versus placebo (hazard ratio [HR]: 0.55; 97.5% confidence interval [CI]: 0.39 to 0.76;

p < 0.001). This treatment effect was established at six months and was sustained for the duration of the study (median duration of more than 2 years)[2,3].

Results of an exploratory subgroup analyses confirmed that treatment with macitentan significantly reduced the risk of morbidity and mortality versus placebo in patients naive to PAH-specific treatment (HR: 0.45; 95% CI: 0.28 to 0.72; p < 0.001) and in patients receiving concomitant PAH-specific treatment (HR: 0.62; 95% CI: 0.43 to 0.89; p = 0.009)[1].

Statistically significant results, favouring macitentan, were also observed for secondary endpoints: i.e. the reduction of PAH related death or hospitalisation for PAH; change in six-minute walking distance ([6MWD] which was maintained for the duration of the study); and WHO FC. See Table 1 for results. Macitentan also improved quality of life as assessed by the SF-36 questionnaire[1–3].

Table 1. Results of primary and secondary endpoints in SERAPHIN, ITT population[1,15].

Endpoint	Macitentan (n = 242)	Placebo (n = 250)	Macitentan versus placebo
Number of events related to PAH or death, as the first event*	76 (31.4%)	116 (46.4%)	HR: 0.55 (97.5% CI: 0.39 to 0.76) p < 0.001
Number of deaths due to PAH or hospitalisation for PAH, as the first event†	50 (20.7%)	84 (33.6%)	HR: 0.50 (97.5% CI: 0.34 to 0.75) p < 0.001
Mean (SD) change in 6MWD (m), from baseline to month six†§	12.5 (83.54)	−9.4 (100.59)	22.8 (97.5% CI: 4.0 to 41.5) p = 0.007
Number of patients with improved WHO FC, from baseline to month six†	54 (22.3%) (97.5% CI: 16.6 to 28.9%)	32 (12.9%) (97.5% CI: 8.5% to 18.4%)	RR: 1.74 (97.5% CI: 1.10 to 2.74) p = 0.0063

* Primary endpoint
† Secondary endpoint
§ Adjusted for baseline 6MWD.

6MWD: six-minute walking distance; CI: confidence interval; HR: hazard ratio; m: metre; n: number of patients; PAH: pulmonary arterial hypertension; RR: risk ratio; SD: standard deviation; WHO FC: World Health Organisation functional class.

3.2 ITCs

Due to the lack of comparable long-term outcomes from studies of comparator ERAs bosentan or ambrisentan, Bayesian ITCs were carried out on the available short-term endpoints[1]. A total of nine studies were included in the analyses. The ITCs did not demonstrate statistically significant differences between macitentan and bosentan or ambrisentan, in the short-term assessments of 6MWD, WHO FC improvement, WHO FC decline and peripheral oedema. Long-term mortality results were only reported in two studies[1]: SERAPHIN[15] and Mazzanti (2013)[16]. However, they did not have common comparators and therefore could not be connected in a network for ITCs[1].

3.3 Safety

Overall, macitentan was well tolerated with a similar incidence of adverse events (AEs) to placebo[1]. In the SERAPHIN study the number of patients who discontinued treatment due to AEs was similar in the placebo group (31 [12.4%]) compared with the macitentan group (26 [10.7%])[1]. Serious AEs (SAEs) were reported less frequently in the macitentan group (n = 109 [45%]) than placebo (137 [55%]).

The most frequently reported SAEs were worsening of PAH (placebo: n = 56 [22.5%]; macitentan: n = 32 [13.2%]) and right ventricular failure (placebo: n = 40 [16.1%]; macitentan: n = 23 [9.5%]). Anaemia as an SAE was reported more frequently in

patients on macitentan but was still uncommon (placebo: n = 1 [0.4%]; macitentan: n = 6 [2.5%])[1].

The Committee for Medicinal Products for Human Use (CHMP) concluded that overall, macitentan seems to have a safety profile similar to that of other ERAs[3].

3.4 AWTTC critique

- Currently, macitentan is the only ERA medicine specifically licensed for combination therapy[1,2].
- The licensing of current PAH therapies is based mainly on demonstrated short-term improvement in exercise capacity assessed by 6MWD[3]. Recognising the limitations of change in 6MWD as a primary endpoint, both the proceedings from the 4th World Symposium on Pulmonary Hypertension, and CHMP, recommend that a composite measure capturing morbidity and mortality should be used as the primary endpoint in future phase III PAH studies[3,17,18].
- CHMP highlight that SERAPHIN is the largest study conducted to date in PAH and included a wide population of PAH patients with different ages, aetiologies, WHO FC and background medications[3].
- "Specific claims on mortality however can only be supported by long-term controlled studies including death as a primary endpoint"[17]. CHMP conclude that while acknowledging the big effort of the company to conduct the largest clinical trial so far in PAH, a mortality claim cannot be included[3].
- Patients who prematurely discontinued the double-blind treatment due to worsening of PAH and patients who completed the SERAPHIN study as scheduled, could enter an open-label extension study, SERAPHIN-OL[1,3]. Results from this extension study however, have not been made available.
- In the absence of any direct comparative data, the applicant company conducted ITCs[1]. Evidence for the efficacy of bosentan and ambrisentan came from short-term studies not designed to assess long-term outcomes. Therefore, comparisons were limited to short-term efficacy endpoints. Further, limitations of the ITCs analyses, acknowledged by the company, included those caused by small patient numbers and heterogeneity in study design, populations and analyses[1]. As a result, the conclusions drawn from the ITCs should be interpreted with caution in light of these limitations.
- CHMP concluded that although there are no major safety concerns related to macitentan, a potential association between macitentan and risk of liver toxicity cannot be ruled out[3]. The Summary of Product Characteristics (SPC) for macitentan has been aligned with that of ambrisentan regarding hepatic safety (contraindication in patients at risk, and recommendation for regular monitoring), as the hepatotoxicity risk seems comparable[2,3].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission[1] describes a cost-minimisation analysis (CMA) of macitentan compared against other licensed ERAs bosentan and ambrisentan in the management of patients with WHO FC II to III PAH. As the company's analysis excludes use of macitentan as an alternative to first-line PDE5i therapy, the economic evidence is restricted to use in a subgroup of its licensed indication[2].

A state-transition model has been developed to represent the clinical pathway of PAH. Patients with WHO FC II or III enter the model in a stable disease state while on ERA treatment, where they may remain or may progress to the next WHO FC category, followed by death[1].

In the absence of direct comparative data for macitentan and other ERAs, Bayesian network meta-analyses have been conducted to provide adjusted ITCs (see Section 3.2). Using random effects models, these indirect analyses estimate there are no statistically significant differences between macitentan and the comparators for short-term symptomatic outcome measures, including 6MWD, changes in WHO FC, and peripheral oedema[1]. Based on these, the company assumes that macitentan and the comparator ERAs have equivalent efficacy in terms of morbidity and mortality. Therefore, progression between stable disease, progressed disease and death for macitentan and each comparator in the economic model is based on time-to-event curves derived from the three-year SERAPHIN study of macitentan[15], which are extrapolated using parametric functions. Rate of treatment discontinuation is also derived from the SERAPHIN trial, and is assumed constant in each modelled cycle[1].

In contrast, AEs in the model are implicitly assumed to differ between macitentan and the comparators. The model considers peripheral oedema and liver toxicity as AEs and the company reports that Bayesian adjusted ITCs of liver toxicity were not possible based on available study data. Crude rates of both peripheral oedema and liver toxicity, derived from the SERAPHIN study for macitentan[15] and from US prescribing information for the comparator ERAs[19,20], have been assumed.

A wide range of resource use and costs associated with ongoing PAH management are included based on study data and company-sought expert opinion. These are assumed the same for macitentan and the comparator ERAs. AE management is informed by expert opinion and costed using published unit costs. Medicine acquisition costs for macitentan are based on a confidential discount on its list price agreed via a Wales Patient Access Scheme (WPAS)[1], and for comparator ERAs are estimated from the British National Formulary (BNF) list prices[21].

The base case CMA considers a time horizon of three years. Costs are accrued in three-month cycles, with those beyond the first year discounted at 3.5% per annum[1].

4.1.2 Results

Results of the CMA are presented in Table 2. Macitentan, at its WPAS-agreed discounted price, is estimated to be cost saving compared with bosentan and ambrisentan at their current list prices. The sole driver of the estimated cost savings is the lower rate of AEs assumed for macitentan compared with the comparator ERAs.

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

Item	Macitentan	Bosentan	Ambrisentan
ERA drug acquisition costs (WPAS)	¶	£46,308	£46,308
Concomitant drug costs	¶	£13,774	£13,774
Administration costs	¶	£147	£147
AE costs	¶	£505	£272
Monitoring and management costs	¶	£4,827	£4,827
Hospitalisation costs	¶	£1,621	£1,622
Costs of progression	¶	£643	£643
Costs of death	¶	£0	£0
Total costs	¶	£67,825	£67,592
Incremental costs: macitentan versus comparator		¶	¶

¶: commercial in confidence figure removed.
AE: adverse events; ERA: endothelin receptor antagonists; WPAS: Wales Patient Access Scheme.

One-way sensitivity analyses include variation in parameter values in ranges of assumed standard errors, and scenario analyses include exploration of the impact of different discount rates, time horizons, proportions of patients with WHO FC II or III at baseline, and source of hospitalisation resource data. All retain the assumption of equal efficacy but with lower rates of AEs for macitentan compared with the other ERAs; therefore, all analyses estimate macitentan to be less costly than the comparator ERAs, are as would be expected from this approach.

4.1.3 AWTTC critique

The company has presented a CMA of macitentan when used as other licensed ERAs are used in practice. The analysis is based around a complex, long-term disease progression model. There are no direct comparative data for macitentan and the comparators; therefore, the company's CMA relies on limited evidence from adjusted ITCs, which the company acknowledges have several limitations (see Section 3.4). The adjusted ITCs estimated no statistically significant differences in short-term symptomatic measures, but credible intervals around all point estimates are very large, reflecting high levels of variance and uncertainty. Furthermore, these analyses of short-term outcomes are assumed to support the assumption of long-term equivalence in the disease progression model. The sole driver of the estimated cost savings with macitentan is its modelled lower rates of AEs compared with bosentan and ambrisentan; however, these rates are based on crude, unadjusted ITCs, which are subject to further limitations and provide no robust evidence of a true incremental benefit of macitentan.

Collectively, the assumption of therapeutic equivalence, required for CMA, is subject to considerable uncertainty, and the inclusion of differential AEs challenges the company's CMA approach. Macitentan is the only ERA with long-term trial-based morbidity and mortality data, and the company suggests assumption of therapeutic equivalence would be conservative in the absence of such data for other ERAs. [Commercial in confidence information removed].

The company suggests macitentan should be considered under the AWMSG policy for appraising ultra-orphan medicines (see Section 6.5).

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 attempt adjusted ITCs. A range of short-term outcomes were assessed from the available data.

Key limitations and uncertainties in the economic evidence include:

- The company's analysis excludes use of macitentan as an alternative to first-line PDE5i therapy. The economic evidence therefore relates to restricted use of macitentan in a subset of its licensed indication[2].
- The CMA framework assumes therapeutic equivalence in all domains of health outcomes. There is a lack of direct comparative data for macitentan and potential comparators, and it is uncertain that the indirect comparative data provided by the company demonstrate therapeutic equivalence required for CMA:
    - The adjusted indirect comparisons relate to short-term symptomatic outcomes, but the disease-progression model assumes equivalence for longer term outcomes. The company suggests this is a conservative approach; however, the relationship between the short-term symptomatic outcomes and longer-term morbidity and mortality is also noted by the company to be uncertain.
    - Credible intervals around all indirect effect size estimates are very large, reflecting the large variance and uncertainty in the ITCs. The extent to which these span clinically meaningful differences in outcomes is unclear.
    - The sole driver of the estimated cost savings with macitentan is its modelled lower rates of AEs compared with bosentan and ambrisentan; however, these rates are based on crude, unadjusted ITCs, which provide no robust evidence of a true incremental benefit of macitentan. The inclusion of differential adverse effects in the model challenges the premise of therapeutic equivalence.
- The sensitivity and scenario analyses provided by the company are of limited informative value. The high degree of uncertainty in the assumptions of equivalent efficacy and improved safety with macitentan compared with other ERAs has not been explored in sensitivity analyses.

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[5], the company report a prevalence of 149 patients with PAH in Wales. A published registry study for the UK and Ireland reports an incidence of 1.1 cases per million persons[22], and an estimated mortality rate of 3.17% has been made, resulting in an estimated 148 PAH patients in Wales each year. This is assumed constant over the next five years.

Based on the National Audit of Pulmonary Hypertension data, 35.25% (52 patients) are estimated to receive ERA treatment (with bosentan and ambrisentan) and be potentially eligible for treatment with macitentan[5]. Uptake of macitentan is assumed to be 40% in year one, rising to 90% in year five, with more rapid displacement of bosentan than ambrisentan. Treatment discontinuation is estimated to be 19.76% based on the rate observed in the SERAPHIN study[1].

Medicine acquisition costs for macitentan are based on a WPAS-agreed confidential discount on its list price, and bosentan and ambrisentan are based on their current BNF list prices. The company assumes that the rates of liver toxicity and/or peripheral

oedema are lower with macitentan compared with the comparator ERAs, as per the economic model.

5.1.2 Results

Based on the confidential WPAS-agreed discount on the list price of macitentan, the net budget impact of the introduction of macitentan in NHS Wales is presented in Table 3. The company estimates annual savings on the introduction of macitentan, due almost entirely to the assumed lower rate of AEs compared with bosentan and ambrisentan.

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

	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of patients on ERA	52	52	52	52	52
Uptake of macitentan	40%	70%	86%	90%	90%
Number of patients treated with macitentan	17	29	36	38	38
Net drug acquisition costs	¶	¶	¶	¶	¶
Net AE costs	−£2,328	−£3,928	−£4,160	−£4,218	−£4,218
Total net budget impact	¶	¶	¶	¶	¶

¶: commercial in confidence figure removed.
AE: adverse event; ERA: endothelin receptor antagonists.

Several scenarios analyses have been conducted. Alternative higher prevalence and incidence rates, based on the trends observed in the National Audit of Pulmonary Hypertension marginally increased the estimated cost savings. Use of higher PAH mortality data from the National Audit of Pulmonary Hypertension and the SERAPHIN study marginally decreased the estimated cost savings; use of the mortality rate estimated from the company's disease progression model also marginally decreased the estimated cost savings. Assuming lower discontinuation rates of 10–15%, based on expert opinion, marginally increased the estimated cost savings. The largest change from the base case estimates presented by the company arose from assuming a higher proportion of patients receive ERA therapy; doubling the proportion (based on expert opinion) doubles the estimated cost savings, as would be expected from a doubling of patient numbers.

5.1.3 AWTTC critique

- The company has adopted a pragmatic approach to estimate the number of patients with PAH eligible for treatment with macitentan. As in the company's economic model, the budget impact analysis excludes use of macitentan as an alternative to first-line PDE5i therapy.
- There are several limitations and uncertainties in the estimated net cost savings:
    - The estimated cost savings are driven almost entirely by the assumed lower rate of AEs with macitentan compared with the comparator ERAs. The AE rates are based on crude, unadjusted ITCs of rates observed in the SERAPHIN study for macitentan and US prescribing information for the comparators, which provide no robust evidence of a true benefit of macitentan regarding AE profile.
    - The assumed reductions in costs as a result of these assumed differential AEs relate to costs of hospitalisation and health care professional contacts, which would not be realised or released as cost savings in practice without a reduction in service provision.

- The company assumes macitentan will preferentially displace bosentan, with complete displacement within two years. The basis of this assumption is unclear, but it is of note that, as modelled, bosentan is assumed to be associated with the greatest AE costs, and displacement of bosentan in preference to displacement of ambrisentan would lead to greater estimated cost savings with macitentan.

- The scenario analyses are of limited informative value. No exploration of the key assumptions driving the estimated cost savings has been conducted.
- Based on the WPAS-agreed price, [commercial in confidence information removed].

5.2 Comparative unit costs

Example annual maintenance costs of macitentan and other treatments licensed for use in PAH are included for reference in Table 4, based on BNF list prices (exclusive of VAT)[21].

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

Medicine	Example regimen	Annual costs*
Macitentan (Opsumit®▼) tablets	10 mg once daily	£28,056
Bosentan (Tracleer®) tablets	62.5 mg to 125 mg twice daily	£19,687
Ambrisentan (Volibris®) tablets	5 mg once daily	£19,687
Riociguat (Adempas®▼) tablets	1.5 mg to 2.5 mg three times per day	£26,003
Iloprost (Ventavis®) nebuliser solution	2.5 micrograms to 5.0 micrograms, six to nine times daily (inhalation)	£7,304 to £21,911
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 SPCs for full dosing details[2,23–31].
*Costs based on BNF list prices 30/07/2015[21]. A confidential discount on the list price of macitentan is available to NHS Wales via a WPAS.

BNF: British National Formulary; SPC: Summary of Product Characteristics; WPAS: Wales Patient Access Scheme.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

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

The company anticipate that macitentan (Opsumit®▼) 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.

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: 6 and 7 July 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 use of macitentan in the given population may meet the criteria for ultra-orphan status. The AWMSG policy defines an ultra-orphan medicine as a medicine that has been granted EMA designated orphan status and is used to treat a condition with a prevalence of one in 50,000 or less in the UK (or 60 patients in Wales). The definition applies to the full population of the licensed indication[32].

Macitentan has been granted orphan status by the EMA for the treatment of PAH[9]. In support of its suggestion that macitentan meets the AWMSG criteria for ultra-orphan status, the company cites several registry studies conducted in different European countries reporting the prevalence of diagnosed PAH to be between 0.3 and 1.3 cases per 50,000 persons[1]. However, based on data from the National Audit of Pulmonary Hypertension, 2013, the prevalence of PAH in Wales is estimated by the applicant company to be 48.7 cases per million population[5], which is approximately equivalent to 150 patients in Wales. As macitentan is licensed only for use in those with WHO FC II and III PAH[2], the number of patients meeting the licensed indication would be lower than this but the prevalence of treated PAH may still exceed the threshold of 60 patients in Wales. In the absence of additional circumstances specific to macitentan, AWTTC therefore consider macitentan may not meet the AWMSG criteria for ultra-orphan status.

REFERENCES

1 Actelion Pharmaceuticals UK Ltd. Form B: Detailed appraisal submission. Macitentan (Opsumit®▼). Jun 2015.

2 Actelion Pharmaceuticals UK Ltd. Opsumit®▼. Summary of Product Characteristics. Jul 2015. Available at: http://www.medicines.org.uk/emc/medicine/28490. Accessed Jul 2015.

3 European Medicines Agency. Assessment Report for Opsumit. Procedure No.: EMEA/H/C/002697/0000. Oct 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002697/WC500160900.pdf. Accessed Jul 2015.

4 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 (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *European Heart Journal* 2009; 30: 2493-537. Available at: http://eurheartj.oxfordjournals.org/content/ehj/30/20/2493.full.pdf. Accessed: Jul 2015.

5 Health and Social Care Information Centre (HSCIC). National audit of pulmonary hypertension 2013. Report for the audit period 2012. 2013. Available at: http://www.hscic.gov.uk/catalogue/PUB13318/nati-pulm-hype-audi-2013-rep.pdf. Accessed Aug 2015.

6 NHS England. Clinical Commissioning Policy: National policy for targeted therapies for the treatment of pulmonary hypertension in adults. May 2014. Available at: http://www.england.nhs.uk/wp-content/uploads/2014/06/a11-ps-b.pdf. Accessed Oct 2015.

7 Galie N, Corris PA, Frost A et al. Updated treatment algorithm of pulmonary arterial hypertension. *Journal of the American College of Cardiology* 2013; 62 (25): Suppl. D60-D72. Available at: http://content.onlinejacc.org/article.aspx?articleid=1790601. Accessed: Jul 2015.

8 Welsh Health Specialised Services Committee (WHSSC). Specialised services policy: drug therapy for pulmonary hypertension CP11. Mar 2013. Available at: http://www.wales.nhs.uk/sites3/documents/898/CP11%20-%20Pulmonary%20Hypertension%20v2.0.pdf. Accessed Jul 2015.

9 European Medicines Agency. Public summary of opinion on orphan designation: macitentan for the treatment of pulmonary arterial hypertension. Procedure No.: EMA/COMP/635474/2011 Rev.2. Mar 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2011/10/WC500116527.pdf. Accessed Jul 2015.

10 All Wales Medicines Strategy Group. Final Appraisal Recommendation - 2508. Ambrsentan (Volibris®▼) 5 mg and 10 mg film-coated tablet. Apr 2009. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/20. Accessed Aug 2015.

11 All Wales Medicines Strategy Group. Final Appraisal Recommendation - 1910. Sildenafil citrate (Revatio®▼) 0.8 mg/ml solution for injection. Dec 2010. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/667. Accessed Aug 2015.

12 All Wales Medicines Strategy Group. Final Appraisal Recommendation - 1010. Sildenafil citrate (Revatio®▼) 20 mg film-coated tablet. Jun 2010. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/273. Accessed Aug 2015.

13 All Wales Medicines Strategy Group. Final Appraisal Recommendation - 2515. Riociguat (Adempas®▼) 0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg film-coated tablets. Sep 2015. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/558. Accessed Nov 2015.
14 All Wales Medicines Strategy Group. Statement of Advice - 68. Bosentan (Tracleer®) 62.5 mg and 125 mg film-coated tablet. Jul 2011. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/68. Accessed Aug 2015.
15 Pulido T, Adzerikho I, Channick RN et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *The New England Journal of Medicine* 2013; 369 (9): 809-18. Available at: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1213917. Accessed: Aug 2015.
16 Mazzanti G, Albini A, Palazzini M et al. A randomized open label study comparing first-line treatment with bosentan or sildenafil in Pulmonary Arterial Hypertension (PAH). *European Heart Journal* 2013; 34 (Suppl 1): 186-7. Available at: http://eurheartj.oxfordjournals.org/content/ehj/34/suppl_1/1063.full.pdf. Accessed: Aug 2015.
17 European Medicines Agency. Guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension. Oct 2009. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/12/WC500016686.pdf. Accessed Aug 2015.
18 McLaughlin VV, Badesch DB, Delcroix M et al. End points and clinical trial design in pulmonary arterial hypertension. *Journal of the American College of Cardiology* 2009; 54 (1): S97-S107. Available at: http://ac.els-cdn.com/S0735109709012091/1-s2.0-S0735109709012091-main.pdf?_tid=723e6978-44ce-11e5-bb72-00000aab0f26&acdnat=1439809097_8094c64ef415a3ddc57bff551af1eedc. Accessed: Aug 2015.
19 Actelion Pharmaceuticals US Inc. Prescribing information for Tracleer (bosentan) 62.5 mg and 125 mg film-coated tablets. 2012. Available at: http://www.tracleer.com/docs/Tracleer_Full_Prescribing_Information.pdf. Accessed Aug 2015.
20 Gilead Sciences Inc. Prescribing information for Letairis (ambrisentan) 5 mg and 10 mg film-coated tablets. Jan 2014. Available at: http://www.gilead.com/~/media/Files/pdfs/medicines/cardiovascular/letairis/letairis_pi.pdf. Accessed Aug 2015.
21 British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. Jul 2015. Available at: https://www.medicinescomplete.com/mc/bnf/current/. Accessed Aug 2015.
22 Ling Y, Johnson MK, Kiely DG et al. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension. Results from the pulmonary hypertension registry of the United Kingdom and Ireland. *American Journal of Respiratory and Critical Care Medicine* 2012; 186 (8): 790-6. Available at: http://www.atsjournals.org/doi/pdf/10.1164/rccm.201203-0383OC. Accessed: Aug 2015.
23 Actelion Pharmaceuticals UK Ltd. Tracleer® 125 mg film-coated tablets. Summary of Product Characteristics. Jun 2015. Available at: http://www.medicines.org.uk/emc/medicine/20423. Accessed Aug 2015.
24 Actelion Pharmaceuticals UK Ltd. Tracleer® 62.5 mg film-coated tablets. Summary of Product Characteristics. Jun 2015. Available at: http://www.medicines.org.uk/emc/medicine/20422. Accessed Aug 2015.
25 Bayer Healthcare Pharmaceuticals. Adempas®▼1.5 mg film-coated tablets. Summary of Product Characteristics. Oct 2014. Available at: http://www.medicines.org.uk/emc/medicine/28741. Accessed Aug 2015.

26 Bayer Healthcare Pharmaceuticals. Adempas®▼ 2 mg film-coated tablets. Summary of Product Characteristics. Oct 2014. Available at: http://www.medicines.org.uk/emc/medicine/28738. Accessed Aug 2015.
27 Bayer Healthcare Pharmaceuticals. Adempas®▼ 2.5 mg film-coated tablets. Summary of Product Characteristics. Oct 2014. Available at: http://www.medicines.org.uk/emc/medicine/28742. Accessed Aug 2015.
28 Bayer Healthcare Pharmaceuticals. Ventavis®. Summary of Product Characteristics. Dec 2014. Available at: http://www.medicines.org.uk/emc/medicine/13743. Accessed Aug 2015.
29 Eli Lilly & Co Ltd. Adcirca®. Summary of Product Characteristics. Oct 2013. Available at: http://www.medicines.org.uk/emc/medicine/23886. Accessed Aug 2015.
30 GlaxoSmithKline. Volibris®. Summary of Product Characteristics. Oct 2014. Available at: http://www.medicines.org.uk/emc/medicine/20848. Accessed Aug 2015.
31 Pfizer Ltd. Revatio®. Summary of Product Characteristics. Apr 2015. Available at: http://www.medicines.org.uk/emc/medicine/17443. Accessed Aug 2015.
32 All Wales Medicines Strategy Group. AWMSG Orphan and Ultra Orphan process. May 2015. Available at: http://www.awmsg.org/awmsgonline/grabber?resId=File%2F1770. Accessed Aug 2015.