All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Sildenafil (Revatio®▼) for the treatment of pulmonary arterial hypertension (WHO functional class II or III) to improve exercise capacity

Pfizer Ltd

Advice No: 1010

Recommendation of AWMSG

Sildenafil (Revatio®▼) is recommended, within its current licensed indication, as an option for use within NHS Wales for the treatment of pulmonary arterial hypertension (WHO functional class II or III) to improve exercise capacity.

AWMSG recommends that its use be restricted to a physician experienced in the treatment of PAH in association with a National Commissioning Group designated expert centre.

AWMSG is of the opinion that sildenafil (Revatio®▼) is not suitable for shared care between primary and secondary care within NHS Wales.

Statement of use:
No part of this advice may be used without the whole of the advice being quoted in full.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday 23rd June 2010

The recommendation of AWMSG is:

Sildenafil (Revatio®▼) is recommended, within its current licensed indication, as an option for use within NHS Wales for the treatment of pulmonary arterial hypertension (WHO functional class II or III) to improve exercise capacity.

AWMSG recommends that its use be restricted to a physician experienced in the treatment of PAH in association with a National Commissioning Group designated expert centre.

AWMSG is of the opinion that sildenafil (Revatio®▼) is not suitable for shared care between primary and secondary care within NHS Wales.

2.0 PRODUCT DETAILS

2.1 Licensed indication

Sildenafil (Revatio®▼) is indicated for the treatment of patients with pulmonary arterial hypertension (PAH) classified as World Health Organisation (WHO) functional class (FC) II and III, to improve exercise capacity[1].

Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease[1].

2.2 Dosing

The recommended dose is 20mg three times a day. Tablets should be taken approximately six to eight hours apart with or without food[1].

2.3 Market authorisation date

PAH WHO FCIII: 28th October 2005[2]
PAH WHO FCII: 7th July 2009[2]

2.4 UK Launch date

6th March 2006[3]

3.0 DECISION CONTEXT

3.1 Background

PAH is a rare, progressive and life threatening disease characterised by an increase in pulmonary vascular resistance leading to right ventricular failure and death[2,4]. The WHO functional classification of PAH, modified from the New York Heart Association (NYHA) is included in appendix 1. Treatments are classified into three main therapeutic classes and include prostanoids, endothelin receptor antagonists (ERAs) and phosphodiesterase-5 (PDE-5) inhibitors. The prostanoids are generally restricted for use in FCIV patients[2,5-6]. There are three ERAs licensed for the treatment of PAH these include; ambrisentan (Volibris®▼), bosentan (Tracleer®▼) and sitaxsentan (Thelin®▼); the latter being restricted for use in FCIII patients[7-9]. Tadalafil and sildenafil are two PDE-5 inhibitors recommended in the European Society of Cardiology (ESC) guidelines for the treatment of PAH. Sildenafil (Revatio®▼) is however the only PDE-5 inhibitor licensed at the time of the company submission. It is a potent and selective inhibitor of cyclic guanosine monophosphate (cGMP) specific PDE-5, the enzyme responsible for degradation of cGMP[1]. This leads to pulmonary vascular smooth muscle relaxation resulting in vasodilation of the pulmonary vascular bed, and to a lesser extent, vasodilation in the systemic circulation[1].

The company estimate of the number of people from Wales with PAH, eligible for treatment in 2009, was 62[2] (notably, this is based on prevalence and incidence data from the Scottish Pulmonary Vascular Unit [SPVU]). On the assumption that 35% of PAH patients are prescribed sildenafil the company estimate 25 patients are likely to receive treatment in Wales in 2010, increasing to 33 patients in 2014[2].

3.2 Comparators

As discussed under section 3.1, the most relevant comparators to sildenafil are considered to be:

FCII and FC III

- Abrisentan
- Bosentan
- Tadalafil (not licensed at the time of this submission)

FCIII only

- Sitaxentan

3.3 Guidance and related advice

- European Society of Cardiology (ESC) and European Respiratory Society (ERS) Task Force Guidelines (2009)[5]. These guidelines for the diagnosis and treatment of pulmonary hypertension have outlined an evidence-based treatment algorithm. This recommends a choice of ambrisentan, bosentan or sildenafil as medicines for initial therapy in the treatment of PAH WHO FCII. As well as these individual medicines sitaxentan, intravenous epoprostenol, or inhaled iloprost are other medicines which are also recommended for initial therapy in the treatment of PAH WHO FCIII. As no head-to-head comparisons among different products are available, no evidence based first-line treatment can be proposed[5]. The choice of drug is dependent on a variety of factors including route of administration, side effect profile, patients' preferences and physicians' experience[5].
- The consensus statement on the management of PAH in clinical practice in the UK and Ireland (2008)[6]
- National Specialised Commissioning Group Guidelines for England (2008) – currently under review[10]
- A commissioning policy document for Wales (Health Commission Wales, 2007) lists sildenafil as first line therapy in newly diagnosed PAH patients unless contraindicated[11]

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

The company submission is based on a 12-week randomised placebo-controlled trial for sildenafil (SUPER-1), an open label 36 month extension study (SUPER-2) and two 12-week randomised controlled studies for ambrisentan (ARIES-1 and ARIES-2). In SUPER-1 (n=277) the primary endpoint of change from baseline in 6-minute walking distance (6MWD) was 45m (placebo-adjusted) for pooled FC in the sildenafil 20mg group. This was comparable to the mean 6MWD of 45m for the 5mg groups in ARIES-1 and ARIES-2 at week 12. No formal indirect comparison analysis was carried out. No major safety concerns were reported in any of the trials.

4.2 Review of the evidence on cost-effectiveness

A rudimentary cost minimisation analysis (CMA) has been conducted to compare sildenafil against ambrisentan. An assumption of equivalence for sildenafil and ambrisentan is made based on a simple, unadjusted comparison of the 12-week, placebo-adjusted increase from baseline in the 6MWD observed with sildenafil in the SUPER-1 trial and the mean average 6MWD observed with ambrisentan in the ARIES-1 and -2 trials.

The analysis suggests that 12 months of treatment with sildenafil is less expensive than with ambrisentan (£6,283 versus £21,970). Cost differences are driven primarily by drug acquisition costs. It should be noted that CMA requires that the comparators are equivalent in all dimensions of health outcome. However, there is little formal evidence of equivalence.

4.3 Limitations of the evidence

- There are no direct comparative data for sildenafil and relevant comparators.
- The economic analysis assumes equivalence between sildenafil and ambrisentan based on a simple comparison of short-term efficacy data. Indirect comparisons have inherent limitations.

5.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

5.1 Clinical evidence

The company submission is based on one randomised placebo-controlled trial (SUPER-1); an open label long-term extension study (SUPER-2) and a brief indirect comparison with ambrisentan using two concurrent placebo-controlled studies (ARIES-1 and ARIES-2)[2].

5.1.1 Placebo Controlled Studies

SUPER-1 was a 12-week multi-centre, randomised, placebo-controlled trial designed to assess the efficacy and safety of three doses of oral sildenafil (20, 40, and 80mg, three times daily) for the treatment of PAH. Of the 207 patients treated with sildenafil, 69 patients received the licensed dose (20mg) and out of these 64 were classified as WHO FCII (n=24) or III (n=40). The primary endpoint was 6MWD at week 12[2]. A statistically significant increase in 6MWD was observed in all three sildenafil dose groups when compared to placebo[1]. Placebo corrected increases in 6MWD were 45m, 46m and 50m for 20mg, 40mg and 80mg respectively, $p<0.0001$[1]. For the 20mg sildenafil treatment group the mean changes in 6MWD from baseline were 58.5m and 30.0m for patients with PAH WHO FCII and III, respectively and the placebo-adjusted mean change in 6MWD was 49.2m ($p<0.001$) and 45.4m ($p=0.003$) for WHO FCII and III, respectively[2]. Only one patient in each FC experienced a decline in FC[2]. After 12 weeks treatment with sidenafil, improvement was seen in all health related quality of life (HRQL) domains of the SF-36 (short form health survey - 36 item) and the EuroQOL 5-Dimensions (EQ-5D) questionnaire and these effects were strongest in domains addressing the physical impact of health on daily activities and the patients overall perception of health. Statistically significant benefits were seen in three areas of the SF-36 including physical functioning, general health and vitality (for more detailed results see Appendix 1, Table 1A).

SUPER-2 was a 36 month open-label extension study designed to assess the safety and toleration of subject optimised treatment regimens. It also provides long term data on the efficacy of sildenafil in PAH WHO FCII and III patients, although this data should be interpreted with caution due to the lack of control group and the open-label design[4]. Patients who completed the 12 week SUPER-1 trial were enrolled. Out of the 259 patients entering the study, 244 were titrated up to sildenafil 80mg, three times daily (unlicensed dose); ten patients received sildenafil 40mg and only five patients received a 20mg dose. The mean change in 6MWD from baseline, at 12 months was provided however this data is confidential[2].

At 36 months, the mean changes in 6MWD were 50m and 45m for baseline FC II and FCIII subjects, respectively[4]. At three years, 62% of FCII patients and 59% of FCIII patients showed an improvement or no change from baseline in FC[4]. Three year survival data were analysed for FCII and FCIII patients randomised to sildenafil treatment in the SUPER-1 study (n=207). In this population, Kaplan Meier estimates of one, two and three year survival were 99%, 91% and 84%, respectively for patients of WHO FCII patients at baseline and 94%, 90% and 81%, respectively for patients of WHO FCIII at baseline[1-2,4].

5.1.2 Indirect Comparisons

In the absence of direct head-to-head trials the company undertook a thorough literature search to identify randomised controlled trials (RCTs) for ambrisentan[2]. Two double-blind, placebo-controlled studies are highlighted in the company submission (ARIES-1 [n=202] and ARIES-2 [n=192][12]); however no formal comparisons using established methods for indirect comparisons have been carried out between the SUPER-1 and ARIES-1/2 trials[2].

5.2 Safety

Sildenafil is well tolerated and adverse events are mild to moderate in intensity. The most commonly reported side effects are headache, back pain, dyspepsia, flushing, dysponea, diarrhoea and blurred vision. In the SUPER-1 trial, six patients were withdrawn from treatment due to adverse events; one in the sildenafil 20mg group for decreased creatinine clearance[2]. The proportion of subjects with treatment-related adverse events and serious adverse events were similar for baseline FCII and baseline FCIII subjects in the 20mg treatment group. In the 20mg group one serious adverse event (left ventricular dysfunction) was assessed as related to sildenafil and ended in permanent discontinuation[4]. In the SUPER-2 study, 22 patients had severe adverse events which were considered to be treatment related; headache being the most commonly reported. It should be noted that in this three year extension study 94% of patients were receiving 80mg sildenafil [2].

In the ARIES-1 and ARIES-2 studies ambrisentan was well tolerated with adverse events being mild to moderate in intensity. Peripheral oedema, headache and nasal congestion were most frequent when compared to placebo. No comparisons were made between ambrisentan and sildenafil[2].

Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 and 2C9, therefore inhibitors and inducers of these enzymes may affect sildenafil clearance. The summary of product characteristics (SPC) should be consulted for contraindications relating to co-administration and for recommended dose adjustments. The efficacy and safety of sildenafil co-administered with other PAH treatments has not been studied in controlled clinical trials[1].

Sildenafil is not recommended in children below the age of 18 years due to insufficient data on safety and efficacy[1].

6.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- The SUPER-1 study includes patients treated with sildenafil 20mg, 40mg and 80mg (three times daily); however the licensed dose is 20mg and therefore results from the 20mg treatment group have been highlighted.
- There are no direct head-to-head comparison trials of sildenafil with ambrisentan or any other PAH treatments. The company have included ARIES-1 and ARIES-2 in their submission; however no formal indirect analysis was carried out[2]. The EPAR recognises that the changes from baseline in 6MWD for baseline FCII and FCIII subjects treated with sildenafil are comparable with the results reported for the ambrisentan subjects[4].
- SUPER-2 was designed to assess the safety and toleration of subject optimised treatment regimens. The long term data on the efficacy of sildenafil in PAH WHO FCII and III patients should be interpreted with caution due to the lack of control group and the open-label design[4]. Furthermore, the extension study is based on treatment with 80mg of sildenafil which is an unlicensed dose[1]. The safety and duration of effect of sildenafil up to one year has therefore only been demonstrated with the 80mg dose.
- ESC guidelines highlight that in clinical practice up-titration beyond 20mg TDS (often 40mg to 80mg TDS) is needed quite frequently[5].
- The Committee of Medicinal Products for Human Use (CHMP) conclude that comparison of baseline characteristics in the SUPER-1 study demonstrates that FCII subjects were clinically distinguishable from FCIII subjects, and had less severe PAH. They also note that FC II and FCIII subjects were also comparable to subjects in the French National Registry and the ambrisentan studies with respect to baseline 6MWD and haemodynamic parameters[4].
- The CHMP state that due to the low number of FCII patients (n=24) recruited to the 20mg dose group in the SUPER-1 study it is difficult to make any robust conclusions with respect to clinical safety[4].
- The European Public Assessment Report (EPAR) for the original licence indication (PAH FCIII) reported several potential risks in relation to safety which included bleeding events, cardiovascular safety, long-term mortality and ocular safety[13]. The EPAR for the license extension (PAH FCII) for these safety concerns reviewed post-marketing safety data and the CHMP conclude that the risk/benefit balance for sildenafil (PAH) remained unchanged[4].
- ESC guidelines highlight that ambrisentan is well tolerated at 5mg dose; although there is an increased incidence of peripheral oedema[5]. Ambrisentan requires only once daily dosing, and also has also data available for up to one year. However, the guidelines also highlight that ambrisentan requires monthly liver function tests; this is not necessary for sildenafil[5].

7.0 REVIEW OF HEALTH ECONOMIC EVIDENCE

7.1 Context

A rudimentary CMA has been conducted to compare sildenafil against the ERA, ambrisentan. The basis of this approach is: ambrisentan was reported to be more effective and less costly than other ERAs in a recent submission to the All Wales Medicines Strategy Group (AWMSG)[14]; AWMSG recommended ambrisentan as a treatment in patients with class II/III PAH[14]; and the assumption that outcomes with sildenafil will be the same as with ambrisentan in the treatment of patients with FCII/III PAH[2]. There are no head-to-head comparative data for sildenafil and ambrisentan, or other treatments for PAH. No attempt has been made in the submission to formally compare data using established methods for indirect comparisons.

The analysis is conducted from the perspective of the NHS, and is stated to be based on treatment of patients within a designated specialist PAH centre. A 12 month time horizon is considered. A summary of the methods employed is presented in Appendix 2.

7.2 Results

The analysis suggests that 12 months of treatment with sildenafil is £15,687 less expensive than with ambrisentan (see Table 1). Cost differences are driven primarily by drug acquisition costs, with minor differences in monitoring costs as a result of the assumed greater need for liver function tests (LFTs) with ambrisentan[2].

Table 1. Cost analysis of 12 months of treatment with sildenafil and ambrisentan[2]

Item	Sildenafil 20mg TDS (cost £)	% of total cost	Ambrisentan 5mg Daily (cost £)	% of total cost	Difference per year (cost £)
PAH Therapy	4,544	72%	20,088	91%	15,544
GP/ Specialist Visits	595	9%	595	3%	0
Warfarin therapy	22	0%	22	0%	0
Monitoring Bloods / Tests	992	16%	1,136	5%	144
Hospital admission	129	2%	129	1%	0
Total	**6,283**	100%	**21,970**	100%	**15,687**

TDS = three times a day

Scenario analyses have been conducted to explore the impact of increasing the assumed rates of clinical worsening, incorporating the costs of subsequent treatment with ERAs (those who experience clinical worsening are assumed to be switched to other ERAs, with a cost based on the mean average annual cost of bosentan, sitaxentan and ambrisentan) and the number of specialist visits and liver function tests, with sildenafil treatment.

Sildenafil remains the least expensive treatment in all scenarios that are considered, as would be expected given that the main cost driver is drug acquisition costs:

i) Increasing the probability of clinical worsening with sildenafil from 5% to 20% – overall cost difference is £15,299 (£6,671 sildenafil versus £21,970 ambrisentan)
ii) Switching the 5% of patients who experience clinical worsening on sildenafil over to ERAs – overall cost difference is £12,299 (£7,049 sildenafil versus £21,970 ambrisentan)
iii) Increasing the probability of clinical worsening with sildenafil from 5% to 20% and these patients switch to ERAs – overall cost difference is £12,233 (sildenafil £9,737 versus £21,970 ambrisentan)
iv) As iii) plus two additional specialist visits and same LFT monitoring for sildenafil as for ambrisentan – overall cost difference is £11,240 (sildenafil £10,730 versus £21,970 ambrisentan).

7.3 WMP critique of the company's economic evidence

Strengths of the economic evidence

- The approach to costing used in the analysis appears reasonable.

Limitations of the economic evidence

- The approach taken assumes that sildenafil and ambrisentan are equivalent in all dimensions of health outcome over a patient's lifetime, including effectiveness (e.g. survival), safety, tolerability, HRQL and patient preferences. Data to support this assumption are lacking, and no formal indirect comparisons of available data with which to judge the assumption of equivalence for sildenafil and ambrisentan, had been provided in the submission.
- The analysis has a 1-year time horizon of analysis. Should the assumption of equivalence in health outcomes over a lifetime be valid, this will only have a consequence on the estimated cost difference.
- WMP has identified a published CMA that employed a formal indirect comparison of 12-16 week data for oral PAH therapies and which lends support to the assumption of similar efficacy for oral agents in the short term (see section 7.4). There are inherent limitations and caveats to indirect comparisons and it should be noted that the 6MWD observed at 12 weeks with ambrisentan 5mg in ARIES-2 was twice that observed in ARIES-1, and no explanation for that finding is provided[15]. Although the CHMP considered these 12-week data were "comparable"[4], treatment for PAH is lifelong. Both drugs have been shown to increase survival rates at three years compared with what would be expected without specific PAH treatment[15-16]. However, no comparative survival analyses have been conducted.
- The CMA approach allows no consideration of any potential differences in patient compliance or preferences relating to the dosing regimens – sildenafil is taken three times a day compared with once a day for ambrisentan.
- The scenario analyses are of limited informative value as they represent hypothetical cost adjustments for scenarios that run counter to the underlying premise of equivalent effectiveness (i.e. if clinical worsening with sildenafil is 20% but only 5% with ambrisentan, the assumption of comparable effectiveness would not hold and a simple cost analysis would be inappropriate).

7.4 Review of published evidence on cost-effectiveness

A recent health technology assessment (HTA) of PAH treatments included sildenafil in its then licensed indication for class III PAH. This concluded that the addition of sildenafil to supportive care was more effective and less costly than supportive care

alone[17]. Comparisons with other agents were not conducted and ambrisentan was not considered in the HTA report[17].

A Canadian population-based CMA of oral therapies for PAH, published in 2009, concluded that sildenafil was the least costly treatment option compared against ERAs including ambrisentan[18]. An indirect comparison of placebo-controlled trials of PAH drugs was conducted for this analysis, which suggested similar clinical efficacy over 12-16 weeks between agents, as indicated by the magnitude of standardised mean differences between active agents and placebos, and non-significant differences between drugs as determined via meta-regression analysis. The authors note that there are caveats to indirect comparisons of trial data[18].

8.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

8.1 Methods

In the absence of Welsh specific data (there is no PAH specialist centre in Wales), prevalence and incidence data are based on estimates of the SPVU[19], which treats all patients with PAH in Scotland. The prevalence is estimated as 26 cases per million population[19], which the company has extrapolated to the Welsh population aged 18 years and older and estimates there would be around 62 patients in Wales with PAH in 2009. The incidence is estimated as 7.6 per million[19], which the company suggests would be around 18 new cases each year[2].

It is assumed that all patients receive treatment. The population of Wales is estimated to grow by 0.2% per annum, and it is assumed that 12% of patients die each year based on a French national registry study that found a one-year survival rate of 88%[20]. On these assumptions of prevalence, incidence and mortality rates, the total number of patients in 2010 is estimated to be 70, rising to 95 in 2014.

Based on company-conducted market research, it is claimed that 35% of UK patients are prescribed sildenafil[2]. This is used as the base case scenario and further scenarios are presented in which sildenafil is assumed to be used in 50% and 75% of patients, with the remainder assumed to be treated with ERAs. Costs considered in this budget impact analysis are composed of drug acquisition costs (with ERA costs based on the mean annual cost of bosentan, sitaxentan and ambrisentan), plus other costs such as monitoring, hospitalisation, warfarin and GP costs, as in the CMA described in section 7.

8.2 Results

Overall costs of the three scenarios, as estimated by the company, are presented in Table 2. These estimates suggest cost savings would be made if the use of sildenafil was increased from 35%. For example, increasing its use from 35% to 50% of patients, would result in cost savings of around £162,500 (£1,143,877 minus £981,400) in 2010, and £220,500 (£1,552,405 minus £1,331,900) in 2014 .

Table 2. Company estimates of overall costs[2]

	2010	2011	2012	2013	2014
Total patient numbers	70	78	84	90	95
Base Case: Sildenafil 35% / ERA 65%	£1,143,877	£1,274,606	£1,372,652	£1,470,699	£1,552,405
Scenario 1: Sildenafil 50% / ERA 50%	£981,400	£1,093,560	£1,177,680	£1,261,800	£1,331,900
Scenario 2: Sildenafil 75% / ERA 25%	£710,605	£791,817	£852,726	£913,635	£964,393

The company has provided an additional analysis based on prevalence figures from a report by Health Commission Wales (HCW) in 2007[11]. This report suggested there could be between 90 and 300 patients in Wales, although at that time less than 100 were being funded for treatment[11]. Therefore, the company has assumed a figure of 100 patients in 2010, adjusted based on a 12% annual mortality rate, and an upper incidence rate of 20 cases per million per year. This results in an estimate of 88 eligible patients in 2010, rising to 220 in 2014. Using these estimates, increasing the use of sildenafil from 35% to 50% of patients would result in cost savings of around £204,260 (£1,438,017 minus £1,233,760) in 2010, and £511,000 (£3,598,702 minus £3,087,540) 2014.

8.3 WMP Critique

The estimation of eligible patient number and overall budget impact appears subject to significant uncertainty. The additional analysis provided by the company, using HCW data from 2007, results in significantly greater estimates of patient numbers and cost savings. The non-drug costs employed in the analyses are those employed in the CMA, which assumes equivalence of sildenafil and ambrisentan in terms of effectiveness, safety and tolerability. The budget impact analysis implicitly assumes that patients remain on sildenafil or ERA treatment throughout the five years, despite that fact that 5% of patients are assumed to experience clinical worsening each year in the CMA, and that no patients receive prostacyclins (parenteral epoprostenol and inhaled iloprost) over the five year period.

8.4 Comparative unit costs

Sildenafil[1] and the ERAs ambrisentan[7] and bosentan[8] are all licensed for use in class II and III PAH. Sitaxentan is licensed for use only in class III PAH[9]. Annual drug acquisition costs at usual recommended maintenance doses and based on British National Formulary (BNF) list prices[21] are presented in Table 3.

Table 3. Example comparator drug costs

Regimen	Example doses	Approximate annual cost[21]
Sildenafil (Revatio®▼)	20mg three times a day	£4,544
Ambrisentan (Volibris®▼)	5mg once daily	£20,088
Bosentan(Tracleer®▼)	125mg twice daily	£19,463
Sitaxentan (Thelin®▼)	100mg once daily	£20,075
This table does not imply therapeutic equivalence of the regimens and doses		

9.0 ADDITIONAL INFORMATION

9.1 Shared care arrangements

Sildenafil (Revatio®▼) should only be initiated and monitored by a physician experienced in the treatment of PAH[1] and is therefore not considered suitable for shared care.

9.2 Previous AWMSG advice

AWMSG issued guidance on the use of ambrisentan (Volibris®▼) in April 2009. This guidance states that ambrisentan should be recommended for the treatment of patients with PAH classified WHO FCII and III, to improve exercise capacity[14].

9.3 Patient Organisation Information

A patient organisation submission was not received.

9.4 Medical expert summary

Medical expert views were provided.

GLOSSARY

Incidence:
The rate at which new cases occur in a population during a specified period[22].

EQ-5D:
EuroQOL 5-Dimensions - this is a measure of health status for use in evaluating health and healthcare. It describes health status according to five dimensions, and provides a simple descriptive profile generating a single index for health status on which full health is assigned to a value of one and death a value of zero. It has been specifically designed to complement other quality of life measures[23].

Prevalence:
The proportion of a population that are cases at a point in time[22].

SF-36:
The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments[24].

WHO/NYHA Functional Classification of PAH[4,6]:

- Class I: PAH without a resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near-syncope.
- Class II: PAH resulting in a slight limitation of physical activity. The patient is comfortable at rest, but ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
- Class III: PAH resulting a marked limitation of physical activity. The patient is comfortable at rest, but less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
- Class IV: PAH resulting in an inability to carry out any physical activity without symptoms. The patient has signs of right heart failure. Dyspnoea, fatigue, or both may be present even at rest, and discomfort is increased by any physical activity.

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Appendix 1. Additional Clinical Information

Table 1A. SUPER-1 (Placebo-controlled trial)

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Outcomes
1,2	Randomised, double-blind, placebo-controlled Multicentre including 25 centres in Europe 12 weeks	277 WHO FCII: n=107 WHO FCIII: n=160	•≥18 yrs •PPH, PAH related to connective tissue disorders and PAH with surgical repair at least 5yrs previously •PAP ≥25mmHg •PCWP ≤15mmHg •6MWD: ≥100 and ≤450m	Male: 25% Mean age: 49yrs Mean 6MWD: 344m Primary PAH: 63% Secondary PAH (non surgery): 30% Secondary PAH (surgery): 7% Mean Borg Index: 3.4 **For 20mg group:** FCII; n=25 FCIII; n=38 (pooled FC): Male: 29% Mean age: 47yrs Mean 6MWD: 346m Primary PAH: 64% Secondary PAH (non surgery): 30% Secondary PAH (surgery): 6% Mean Borg Index: 3.8	Sildenafil (TDS): 20mg; n=69 FCII; n=24 FCIII; n=40 40mg; n=67 80mg; n=71 Placebo (TDS); n=70 Concomitant medication: Patients were allowed to take anticoagulants i.e. warfarin), antihypertensives (i.e. CCB and diuretics) and antiarrhythmic (digoxin)	**Primary Endpoint at week 12:** (20mg group) **Change in 6MWD from baseline (mean±SD):** Pooled FC: 41.3±54.8m FCII: 58.5±55.6m FCIII: 30.0±52.7m **Placebo-adjusted mean change in 6MWD from baseline:** Pooled FC: 45.3 (95% CI; 20.5, 77.0, p=0.0001) FCII: 49.2 (95% CI; 21.5,77.0, p<0.001) FCIII: 45.4 (95% CI: 15.6, 75.3, p=0.003) **Secondary Endpoints at week 12:** (20mg group) **Change in FC:** FCII: FC improved in 17% of patients; there was no change in 78% patients and FC was worse in 4% patients FCIII: FC improved in 30% of patients; there was no change in 68% patients and FC was worse in 3% patients **Mean change in Borg Dysponea Index:** FCII: -0.5±1.5 FCIII: -1.0±1.7 **Change in Haemodynamic measurements** (pooled FC): Mean change PAP (mmHg±SD): -2.1±8.8 Mean change RAP (mmHg±SD): -0.8±4.6 Mean change in cardiac output (L/min±SD): 0.39±1.03 Mean change PCWP (mmHg±SD): -0.2±5.2 Mean change SAP (mmHg±SD): -2.6±10.1 **Mean change in QoL from baseline to week 12 for pooled FC (placebo [n=70] versus sildenfil [n=200]):** **SF-36:** physical functioning: 4.5 vs 13.7 (p<0.001); role-physical: 15.4 vs 19.8; bodily pain: 4.9 vs 7.1; general health: 0.3 vs 8.0 (p<0.001); vitality: 5.5 vs 11.7 (p<0.5); social functioning: 7.3 vs 12.9; role-emotional: 12.3 vs 14.7; mental health: 5.3 vs 9.2. **EQ-5D:** current health index: 0.6 vs 7.9 (p<0.01); utility index: 0.005 vs 0.101 (p<0.01).

6MWD: 6 minute walk distance; CCB: calcium channel blockers; CI: confidence interval; EQ-5D: EuroQOL 5-Dimensions; FC: functional class; m: meters; PAH: pulmonary arterial hypertension; PAP: pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PPH: primary pulmonary pressure; QoL: quality of life; RAP: right arterial pressure; SAP: systemic arterial pressure; SD: standard deviation; SF-36: Short Form health survey - 36 item; TDS: three times daily; vs: versus; WHO: World Health Organisation; yrs: years.

Appendix 2. Additional Health Economic Information

Base Case Model		Appropriate?
Comparator(s)	Sildenafil compared against ambrisentan	Basis of this comparison is that ambrisentan was reported to be more effective and less costly than other ERAs in a recent submission to AWMSG[14]; AWMSG recommended ambrisentan as a treatment in patients with class II/III PAH[14]; and the assumption that outcomes with sildenafil will be the same as with ambrisentan in the treatment of patients with FCII/III PAH[2].
Population and setting	Patients with class II or III PAH, with treatment based in a designated PAH specialist centre.	Yes
Model type and description	Simple CMA	CMA requires that the comparators are equivalent in all dimensions of health outcome. There is little formal evidence of equivalence.
Perspective	Considers direct medical costs only, from perspective of NHS Wales.	Yes
Time Horizon	One year	No, patients with PAH are expected to survive for longer than 1 year, and treatment is life-long.
Discount rate	N/A due to one year time horizon	Yes, given the company's choice of a 1-year analytic time horizon
Efficacy	An assumption of equivalence for sildenafil and ambrisentan is made based on a simple, unadjusted comparison of the 12 week, placebo-adjusted increase from baseline in the 6MWD observed with sildenafil in the SUPER-1 trial and the mean average 6MWD observed with ambrisentan in the ARIES-1 and -2 trials.	There are no head-to-head comparative data for sildenafil and ambrisentan, or other treatments for PAH. No attempt has been made within the submission to formally compare data using established methods for indirect comparisons. A published CMA employed an indirect comparison of 12-16 week data, and concluded similar clinical efficacy between oral agents[18] (see section 7.4). However, there are some inherent limitations to indirect comparisons. It is of note that the 6MWD observed at 12 weeks with ambrisentan 5mg in ARIES-2 was twice that observed in ARIES-1, and no explanation for that finding is available[15]. It is therefore unclear whether the assumption of equivalence, based on simple, unadjusted comparison of the 12-week SUPER-1 data for sildenafil with that observed in the combined ARIES-1 and -2 studies for ambrisentan, is appropriate. Although the CHMP considered these 12 week data were "comparable"[4], treatment for PAH is lifelong. Both drugs have been shown to increase survival rates at three years compared with what would be expected without specific PAH treatment$_1$[5,16]. However, no comparative analyses have been conducted.
Adverse effects	Not included	Only if the assumption of equivalence in adverse event rates holds.
Utility values	Not included	Only if assumption of equivalence holds.
Resource use and costs	Relate to PAH drug costs, monitoring costs, other GP visits, and warfarin therapy. Sources include a 2009 Health Technology Assessment of PAH treatments[17], and a 2008 UK consensus guideline[6].	Yes
Model Provided?	N/A	N/A
Other considerations	N/A	N/A
6MWD: 6 minute walk distance; AWMSG: All Wales Medicines Strategy Group; CHMP: Committee of Medicinal Products for Human Use; CMA: cost minimisation analysis; ERA: Endothelin receptor antagonist; FC: functional class; PAH: pulmonary arterial hypertension.		