EXECUTIVE SUMMARY

The focus of this submission is on the clinical and cost-effectiveness of bosentan in patients with New York Heart association [NYHA]/World Health Organisation [WHO] functional class III pulmonary arterial hypertension

Background and Impact of Pulmonary Arterial Hypertension (PAH)

- Pulmonary Arterial Hypertension (PAH) is a rare but devastating disease that leads to premature death. It is characterised by elevated pulmonary vascular resistance leading to increased right heart pressures and right heart failure.
- PAH can either be classified as idiopathic (iPAH) or associated with other conditions such as connective tissue disease (CTD), congenital heart disease (CHD) or human immunodeficiency virus (HIV). In clinical practice, patients with PAH are graded according to the underlying pathology of the disease (WHO classification) and the degree of functional disturbance (NYHA/WHO).
- The prevalence of severe PAH in the population (i.e. those in WHO classes III and IV) is low and has been estimated at 30 to 50 cases per million. Based on current population figures and an 80:20 ratio between classes III and IV (see Appendix 2), it is estimated that there are 1,745 PAH adult patients with WHO class III PAH in England and Wales. This is clearly an orphan disease.
- The estimated median survival in a population of WHO class III iPAH patients treated only with palliative care is 2.6 years from the time of diagnosis, which is comparable to certain advanced cancers.

Symptoms and Diagnosis

- Patients with early PAH are often asymptomatic or have mild, non-specific symptoms such as breathlessness which can be incorrectly attributed to other more common conditions such as asthma. This can lead to delays of up to 3 years for patients to receive an accurate diagnosis.
- PAH is a rapidly progressive disease and once symptomatic, patients experience fatigue, dyspnoea at rest, chest pain and syncope, to an increasingly disabling extent. The disease therefore has a severe impact on quality of life (QoL).
- Definitive diagnosis is obtained by the measurement of right heart pressures via right heart catheterisation. Other clinically meaningful endpoints used in clinical trials include the six-minute walk test [6MWT] (the distance walked in 6 minutes– a direct measure of functional impairment), time to clinical worsening (including death and need for transplantation) and right heart haemodynamics.
- Potential delays in diagnosis coupled with the poor prognosis of this disease, highlight the urgency with which patients need to be treated, once correctly diagnosed.

Management of PAH

- The pathophysiology of PAH is characterised by vasoconstriction, remodelling of the pulmonary vessel wall and fibrosis. Optimal therapy should therefore be effective in targeting all of these changes.
- The objectives of treatment are to improve survival and, via relief of symptoms and an increase in functional capacity, to improve the quality of life of patients.
- From the mid-1990s until 2002, standard care was palliative, supportive measures plus the option for continuous i.v prostaglandins (PGs) usually i.v. iloprost. This treatment paradigm is termed ‘historic care’ for the purpose of this submission, and when bosentan was launched this was the contemporary comparator.
- The full range of targeted therapies (endothelin receptor antagonists, PGs (i.v or inhaled) and phosphodiesterase-5 inhibitors) are now regarded as standard care for severe PAH. These treatments differ significantly in their mode of action and are not all clinically equivalent, with differences in the evidence base supporting their different licensed indications. As the overall aim of treatment is to improve survival, the availability of long-term outcome data should be a critical consideration.

Clinical Effectiveness of bosentan

- Bosentan is the only oral, dual endothelin receptor antagonist indicated for the treatment of PAH to improve both exercise capacity and symptoms in patients with WHO class III status.[1]
- Bosentan has re-modelling, anti-inflammatory, anti-fibrotic and vasodilator properties and as such targets the vascular intimal changes associated with the pathogenesis of PAH.
- The efficacy of bosentan has been consistently demonstrated in patients with PAH of multiple aetiologies via both randomised, controlled trials (RCTs) and long-term observational studies.

Short-term Randomised Controlled Trials (RCTs)

- Two pivotal, randomised, double-blind, placebo-controlled, trials of bosentan showed statistically significant improvements at 12 and 16 weeks in:
  - The primary endpoint of the 6MWT, with a mean difference of 76m and 44m between those treated with bosentan versus placebo (p=0.021, p<0.001 respectively).[2,3]
  - Secondary endpoints including time to clinical worsening (p=0.033, p=0.002 respectively).[2,3]

Long-term observational studies

- Conducting long-term, placebo-controlled trials in PAH is not feasible for ethical reasons.
- On completion of the two shorter-term, pivotal placebo-controlled trials, patients were all switched to bosentan and prospectively followed up in an open-label manner to assess long-term outcomes.

  Survival estimates were:
  - [Information removed – academic in confidence] [4]
  - 96%, 89%, 86% at 1, 2 and 3 years, in a sub-group analysis of the iPAH patients compared to a predicted survival of 69%, 57%, 48% respectively for patients treated with supportive care.[5]
  - 85.9% and 73.4% at 1 and 2 years, in a sub-group analysis of the patients with PAH associated with CTD (a patient cohort that responds poorly to PAH therapy).[6] These rates are significantly higher than historic norms.
- An RCT of oral bosentan versus i.v PGs, administered on a 24 hour, continuous basis, is not feasible for practical and ethical reasons.
- The cohort of WHO class III iPAH patients treated with bosentan first line within the pivotal RCTs, was compared with similar patients treated with i.v PGs (historic standard of care) within the same centres.[7] Survival estimates at 1 and 2 yrs were 97% and 91% respectively in the bosentan cohort and 91% and 84% in the PG cohort. While the patients in the two groups were similar, there were some differences in haemodynamics, suggesting that the i.v. PG group were more severe. Cox regression analysis adjusted for these differences, and no evidence was found to suggest that initial treatment with bosentan adversely affected outcome when compared with i.v PGs.

Efficacy in subgroups

- Despite the difficulties in conducting trials in this orphan disease area, where patient numbers are very low, there is a wealth of consistent data for bosentan. Efficacy of bosentan has also been demonstrated in patients with PAH of multiple aetiologies including PAH associated with CTD, CHD and HIV:
  - In one centre, a comparison was made of 'historic' versus 'modern' treatment outcomes.[8] Patients with scleroderma related PAH, who had received historic care (supportive care, plus PGs in approximately 50% of patients) were matched with a cohort of patients given bosentan first-line. Survival in the bosentan group was 81% and 71% compared to 68% and 47% in the historic group, at 1 and 2 years respectively (p=0.016).
  - A 16-week double-blind RCT showed bosentan to significantly improve pulmonary vascular resistance (p=0.0383) and exercise capacity (p=0.008) in patients with Eisenmenger related PAH (WHO class III).[9]
  - A 16-week prospective, non-comparative study in 16 HIV patients, demonstrated a statistically significant improvement in the 6MWT of 91m from baseline (p<0.001). 88% of patients showed an improvement from baseline of at least one functional class.[10]

Quality of Life (QoL)

- A 6-month, open-label study in bosentan-treated patients with iPAH and PAH associated with CTD (WHO class III or IV), resulted in statistically significant improvements in SF-36 scores at 3-months (all p values $\leq$0.005), which were maintained throughout the study period.[11]

Safety and Tolerability of bosentan

- Bosentan has a well-documented safety profile. [Information removed – commercial in confidence] of which nearly 5,000 patients have been included in the EU post-marketing surveillance programme.[12,13]
- Bosentan has been associated with elevations in liver aminotransferases which are dose dependent and, in most cases, reversible.[1]

Cost-effectiveness of Bosentan

- A discrete event simulation model was used to evaluate the cost-effectiveness of bosentan as a first-line therapy for patients with PAH (WHO class III) compared with historic care and with supportive therapy.
- The analysis has been carried out for the two main sub-groups of patients, i.e. iPAH and PAH associated with CTD. There is insufficient data to make such calculations in the other aetiologies, but it is proposed that since these two sub-groups represent the majority of patients, they should be considered reflective of the entire PAH, Venice Category 1 group.
- Constructing a cost-effectiveness analysis for any therapy within PAH is complicated by the ethical limitations of clinical trial design. However, patients within the two pivotal RCTs have been followed up for approximately 2 years and the time to clinical worsening has been recorded. As surrogate endpoints such as the 6MWT are not suitable to be used as predictors of mortality, time to clinical worsening has been used to construct this model.
- The model outputs showed that:
  - Bosentan is a cost effective advanced therapy for PAH. Compared with historical care, it has a mean cost per quality adjusted life year (CPQ) of £20,000 for patients with iPAH, when used as first-line therapy. This value is £15,000 for patients with PAH associated with CTD.
  - The 95% confidence interval in CPQ when comparing bosentan to historical care in iPAH ranged from £16,000 to £38,000. For patients with PAH associated with CTD these values were £11,000 to £29,000.
  - Were all active treatments for patients with PAH to be withdrawn as therapeutic options within the NHS, the mean CPQ of bosentan compared with supportive therapy would be £82,000 for patients with iPAH and £78,000 for patients with PAH associated with CTD. Given the high medical need and the clear mortality benefit of some of the interventions, this 'withdrawal option' should not be considered acceptable within the NHS. It would represent a regression to treatment standards of the early 1990s.
  - When compared with supportive therapy alone the 95% confidence interval ranged from £60,000 to £188,000 for patients with iPAH, and from £54,000 to £184,000 for patients with PAH associated with CTD.

Budget Impact for the NHS

- [Information removed – commercial in confidence]
- The net budget impact of treating the remaining eligible patients with PAH WHO functional class III with first line bosentan is a maximum increment of around £16.4million, spread over 5 years e.g. £3.2M/Yr.
- There are significant variations in treatment rates across the UK. Increasing access to treatment will require investment in infrastructure and capacity to deliver a service with equitable distribution across England and Wales.

Conclusions

- Bosentan is the only oral therapy indicated for the treatment of PAH to improve both exercise capacity and symptoms in patients with WHO class III status.
- Bosentan has consistently been shown to be effective and well tolerated in the short and long-term, in patients with PAH of multiple aetiologies. Bosentan has been shown to:
  - Improve exercise capacity and symptoms in patients with iPAH (WHO class III), as well as those with PAH associated with CTD and CHD in RCTs.
  - Delay the time to clinical worsening and improve QoL
  - Improve long-term outcomes up to 3 years.
- In comparison to established care when bosentan was launched (supportive therapy plus a proportion of i.v PG use), bosentan as first-line therapy has a mean CPQ below £20,000 for those patient sub-groups in whom such a calculation was feasible.

In conclusion, this submission demonstrates that the evidence supporting the use of bosentan together with the ease of oral administration makes it a desirable, cost-effective choice for first-line treatment of patients with severe PAH. This treatment gives patients the potential for a better, longer future. Treatment with supportive care alone, is no longer a reasonable option.

References

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