

**Assessment of the cost-effectiveness of ambrisentan
(Volibris®) for the treatment of patients with Functional Class
II or III Pulmonary Arterial Hypertension (PAH)**



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Summary

1. Ambrisentan is a non-sulphonamide, non-selective, oral, endothelin receptor antagonist (ERA) licensed for treatment of patients with Functional Class (FC) II/III PAH whose current treatment options include the phosphodiesterase type 5 (PDF-5) inhibitor, sildenafil, the alternative oral ERAs bosentan and sitaxentan and the prostacyclin therapies, epoprostenol and inhaled iloprost.
2. In October 2008, Glaxo SmithKline, Ireland submitted an economic evaluation designed to examine the cost-effectiveness of ambrisentan compared to existing treatment strategies for the patient population with FC II/III PAH, to support its application for reimbursement under the High Tech Drugs Scheme. The advantages of ambrisentan in terms of reduced risk of hepatotoxicity and drug interactions were incorporated into the cost-effectiveness analysis which was conducted from the perspective of the Health Services Executive (HSE).
3. The cost effectiveness of ambrisentan was demonstrated using a discrete event simulation (DES) model to analyse the potential effects of ambrisentan on several clinical measures, cost and survival in patients with PAH over a 5 year time horizon. Clinical parameters associated with improvement in the status of patients with PAH include the 6MWD (this is the distance patients are capable of walking in 6 minutes and is a relatively sensitive marker of exercise capacity), time to clinical worsening (TCW), a change in functional class (FC), and a number of haemodynamic parameters.
4. The ambrisentan efficacy outcomes for the model were derived from a combination of the 2 pivotal, phase III, randomised, double blind, placebo controlled trials, namely ARIES-1 (n=202) and ARIES-2 (n=192). In the combined analysis, ARIES-C, the mean baseline 6MWD (mean±SD) was 344.6 ± 80.1 metres (ARIES-1 of 341.0 ± 75.80 and ARIES-2 of 348.4 ± 84.46). Results for the placebo group showed a mean decrease in 6MWD of 9.0 metres, whereas each ambrisentan group demonstrated an increase in 6MWD of 35.7 metres and 43.6 metres for the 5mg and 10mg groups respectively. Data from an open-label extension of the ARIES trials (ARIES-E) at 48 weeks provided the 6MWD model input data rather than the 12 week data. While the review group had concerns over the use of unpublished, observational data, justification was based on the maintenance of improvement in 6MWD at 48 weeks. Data inputs from the secondary end-point parameters were derived from in-house analysis of patient level data or supportive analyses.

5. The use of a discrete event simulation model necessitated transformation of the 6MWD data. The absolute change in terms of an increase in 6MWD was not used for the model – non-inferiority as compared to the comparator ERAs was assumed. The data was transformed using a logistic regression analysis to obtain a treatment coefficient for ambrisentan and the comparators. To do so, individual trial data for ARIES 1 and 2 patients was analysed to determine the percentage of patients whose 6MWD increased or decreased. Treatment coefficients computed for the comparators were based on mathematical adjustments rather than absolute change in 6MWD derived from clinical trials.
6. One of the main drivers of the model was hepatotoxicity with estimated rates of 3%, 11.6% and 5% for ambrisentan, bosentan and sitaxentan respectively. The presence of raised liver enzymes resulted in changes in therapy with associated costs and consequences. Differences in cost consequences between ambrisentan and the comparators arose as a result of switching to alternative more expensive treatments i.e. prostacyclin agents. The decrements in quality of life for clinical worsening events were assigned utility values and the incremental QALY gain for ambrisentan versus bosentan and sitaxentan was 0.12 and 0.06 respectively.
7. Data was presented on the incremental cost effectiveness ratio (ICER) from the HSE perspective. The model estimated that ambrisentan was dominant compared to both bosentan and sitaxentan, although more so to bosentan due to the higher incidence of elevations in liver enzymes. Over the five years, treatment with ambrisentan was estimated to result in cost savings of approximately €28,000 and €8,000 versus bosentan and sitaxentan respectively.
8. One way deterministic sensitivity analyses demonstrated that the model was sensitive to changes in the price of ambrisentan, utility values associated with prostacyclin treatment, and rates of hepatotoxicity. The PSA showed the probability that ambrisentan was dominant compared to bosentan and sitaxentan was 0.86 and 0.73 respectively. It also estimated that the probability that ambrisentan was cost effective i.e. under the €45,000/QALY threshold was 0.87 and 0.77 respectively.
9. The review group considers that the available evidence suggests that ambrisentan represents a cost-effective alternative for treating patients with PAH with FC II or III disease as compared to bosentan and sitaxentan. The clinical problems of hepatotoxicity encountered with the alternative ERAs is acknowledged to impact negatively on the quality of life and outcomes of patients in the clinical setting. The cost effectiveness of ambrisentan is very sensitive to the assumption of cost equality with the comparator ERAs. Therefore, pricing of ambrisentan at or below the current price of comparator ERAs would maximise cost-effectiveness.