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Title **Clinical and Cost Effectiveness of Epoprostenol, Iloprost, Bosentan, Sitaxentan and Sildenafil for the Treatment of Pulmonary Arterial Hypertension within Their Licensed Indications: A Systematic Review and Economic Evaluation**

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Aim

To investigate the clinical and cost effectiveness of epoprostenol, iloprost, bosentan, sitaxentan, and sildenafil in treating adults with pulmonary arterial hypertension (PAH) within their licensed indications.

Conclusions and results

All 5 technologies, when added to supportive treatment and used at licensed dose(s), were more effective than supportive treatment alone in randomized controlled trials (RCTs) that included patients of mixed functional class (FC) and types of PAH. Current evidence does not allow adequate comparisons between the technologies nor for the use of combinations of the technologies. Independent economic evaluation suggests that bosentan, sitaxentan, and sildenafil may be cost effective by standard thresholds and that iloprost and epoprostenol may not be. The use of the most cost-effective treatment would reduce costs for the NHS. This assessment included 20 RCTs, mostly comparing one of the technologies added to supportive treatment with supportive treatment alone. Four published economic evaluations were identified. None produced results generalizable to the NHS. There was no consensus in the industry submissions on the most appropriate model structure for technology assessment. Improvement in 6-minute walk distance (6MWD) was seen with intravenous epoprostenol in primary pulmonary hypertension (PPH) patients with mixed FC compared with supportive care (58 meters; 95% CI 6-110). For bosentan compared with supportive care, the pooled result for improvement in 6MWD for FCIII patients with mixed PAH was 59 meters (95% CI 20-99). For inhaled iloprost, sitaxentan, and sildenafil no stratified data for improvement in 6MWD were available. The odds ratio (OR) for FC deterioration at 12 weeks was 0.40 (95% CI 0.13-1.20) for intravenous epoprostenol compared with supportive care. The corresponding values for inhaled iloprost (FCIII PPH patients; licensed indication), bosentan, sitaxentan (FCIII patients with mixed PAH; licensed indication), and sildenafil (FCIII patients with mixed PAH; licensed indication) were 0.29 (95% CI 0.07-1.18), 0.21 (95% CI 0.03-1.76), 0.18 (95% CI 0.02-1.64) and [Commercial-in-confidence information has been removed] respectively.

Recommendations

This report summarizes the best available evidence and discusses its implications, but does not include recommendations about policy or clinical care.

Methods

Systematic reviews of RCTs and economic literature, along with a model-based economic evaluation, were carried out. Electronic databases were searched up to February 2007. Industry submissions to the National Institute for Health and Clinical Excellence were reviewed.

Further research/reviews required

Long-term, double-blind RCTs of sufficient sample size need to directly compare bosentan, sitaxentan, and sildenafil, and evaluate outcomes including survival, quality of life, maintenance on treatment, and impact on the use of resources for NHS and personal social services. Possible differences in treatment effects between subcategories of PAH and between patients of different FC at baseline should be investigated within and across these trials. More RCTs need to evaluate combinations of the technologies versus monotherapy, and studies investigating the feasibilities of replacing an ongoing treatment that failed to provide adequate control of the disease with a new treatment rather than adding the new treatment to the existing treatment.

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