British Cardiovascular Society

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British Cardiovascular Society response to NICE Draft Pulmonary Arterial Hypertension Report: "Clinical and cost effectiveness of treatments for pulmonary arterial hypertension (PAH) within their licensed indications"

16 September 2007

There are inevitable limitations when assessing health technologies for pulmonary arterial hypertension (PAH) because of limited randomised controlled trial (RCT) data in a rare disease. This particularly so in PAH because it is a heterogeneous condition where there are multiple causes and individual patients follow a widely variable course which is lethal in the majority. The health economic model has been constructed from RCT data from trials up to 16 weeks in duration. The report is hampered by being unable to present a lot confidential data which has been used by the assessment team and is only accessible to NICE. The most important issues are:

1. **The health economic model does not represent real-world clinical practice.** Clinical decisions about patients are made by physicians based on evidence from RCTs and disease registries, the cause of PAH, the age of the patient (the young and old having a worse prognosis), the severity of PAH, other comorbid diseases, carer support, patient preferences, and eligibility for clinical trials.
2. **The report has only examined data up to 16 weeks on treatment in RCTs. This is most disappointing since valuable peer-reviewed long-term data has been ignored.** The physician and their patient expect survival well beyond 16 weeks in most cases. Roughly 70 – 80% of patients survive 3 years at least. The report does not include registry data which provides long-term follow-up. It is extremely unreliable and dangerous to recycle or extrapolate data beyond the period of RCTs in such a disease. Furthermore, given the underlying pathophysiology of cell proliferation in PAH, RCTs of this duration are too short to identify differences between technologies which may impact significantly on later clinical outcomes. For this reason it would be misleading to assume that all the technologies being assessed are similarly effective based on 16 week data.
3. **The number of patients who need this therapy in very small in NHS terms.** In England 1246 patients were on treatment on 31st March 2007. Even if this number were to double or triple the number of patients is very small. **Treatment is prescribed by expert designated centres** who ensure that prescriptions are only provided to patients who will benefit from these technologies. Such an approach ensures the best clinical outcomes.

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4. The emergency treatment for severe PAH, Epoprostenol, comes out most expensive. In considering its case in the appraisal, it should be emphasized that it is the only treatment which reduces mortality in a RCT and remains the "gold standard" for severe disease.
5. **The health economic model is biased towards over-emphasising the cost difference between technologies.** This overrides important clinical differences between the technologies. Examples of this are survival in registry data, secondary end point data which have varied between RCTs and individual pharmacological responses:
   a) Survival has been reported for Epoprostenol and bosentan at licensed doses but not for sildenafil, where data was gathered for 80 mg TDS rather than the licensed 20 mg TDS (these doses had statistically different haemodynamic effects).
   b) Secondary end points such as time to clinical worsening are positive with some agents and not others. Although this end point has not been used in all the trials and even in the trials it has been used its definition varies, it nevertheless provides important clinical outcome information which deserves attention.
   c) It is clear that some patients respond better to one of these three classes of technologies than the others. Thus for individual patients there are important differences in clinical outcomes. In part this is due to differences in the cause of PAH , very different outcomes in different sub groups of PAH (not considered in this report) and pathophysiology.

In summary, while this report suggests differences in cost-effectiveness between different technologies in PAH, we believe that the assumptions of the health economic model and its failure to include published long-term follow-up data in the analysis mean that *it is not sufficiently robust to identify any significant differences in cost effectiveness*.

The imposition of treatment priorities from the NICE Appraisal Committee based on this cost effectiveness data may result in worse clinical outcomes in a patient population which requires individually tailored therapy managed by high volume expert designated centres.

[redacted], on behalf of British Cardiovascular Society
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