2 October 2007

Drugs for the treatment of pulmonary arterial hypertension - Assessment group's response to the comments from consultees on the assessment report

The assessment group appreciates the comments submitted by consultees and commentators on the assessment report and would like to respond to a few general issues that were raised by various consultees and commentators. The responses are listed as bullet points below.

- **Comparisons between the technologies under assessment**

  Clinical effectiveness

  The assessment group has repeatedly emphasised in the assessment report and its protocol that only data from randomised controlled trials that provided head-to-head comparisons of the technologies were to be considered in the assessment of one technology against another. Given the paucity of such evidence no conclusion about the effectiveness of one technology over another can be drawn. As such, head-to-head trials were highlighted as one of the top priorities for future research in the report. Indirect comparisons and mixed treatment comparisons between the five technologies were neither planned nor undertaken. These were unlikely to produce any conclusive results given the amount of evidence currently available. Furthermore such analyses could be potentially inappropriate due to the differences in trial design and study population between the technologies, and the different place of some of the technologies in the treatment pathway. The same cautions apply when any inference with regard to the relative effectiveness between the technologies is made on the basis of data from placebo-controlled trials of individual technologies.

  Cost-effectiveness

  The assessment group has also repeatedly stressed in the assessment report that the independent economic assessment only compared each technology plus supportive care to supportive care alone and was not designed for direct comparison between the technologies. It is inappropriate to compare the ICERs for one technology to that of another technology.

- **Making recommendation regarding treatment choices and service provisions**

  The assessment report aims to critically appraise and synthesise the best available evidence pertinent to the decision problems defined in the appraisal scope and the assessment report protocol. It is beyond the assessment report's remit to make any recommendation

regarding treatment choices and service provisions for the technologies being assessed. In fact, the National Coordinator Centre for Health Technology Assessment who commissioned the report on behalf of the Department of Health explicitly requires that technology assessment reports '*do not make recommendations about policy or about clinical care*'. The only recommendations that were made in the assessment report are the priorities for future research.

- **Limitations defined by the scope for the technology appraisal**

  The primary purpose of the assessment report is to provide an independent evaluation of evidence to help the NICE appraisal committee in reaching their decision. As such the scope of the assessment report has to be in keeping with the scope of technology appraisal. It is therefore inappropriate for the assessment report to consider issues that are beyond the scope of the technology appraisal.

- **Use of functional class (FC) change as the key outcome measure and extrapolation of data from short-term trials to an extended time horizon in economic model**

  The challenge in assessing the cost-effectiveness of the technologies for the treatment of PAH is well acknowledged due to a number of reasons but most notably the lack of appropriate data. The approach to use change in FC as the key outcome measure along with the need for making various assumptions and extrapolating short-term data are some practical solutions in the absence of better alternatives. The assessment group has presented these explicitly and also carried out extensive sensitivity analyses in the assessment report. In addition the assessment group also highlighted the possibility of additional uncertainty not captured by these sensitivity analyses. Acknowledging the limitation associated with these uncertainties, the assessment group believe the independent economic assessment is a valuable contribution for advancing economic evaluation in this field and would welcome further development of such evaluations in the future as a result of increased availability/accessibility of data.

- **Assumption related to no improvement of functional class (FC) on treatment beyond the first cycle (12 weeks) of the economic model**

This issue was considered by the assessment group during the construction of the assessment group model. In particular, data from long-term follow-up of bosentan and sitaxentan trials were considered. In the study by Sitbon et al 2007 (cited in the comments from Actelion), [redacted]. However, cautions in interpreting the apparent long-term FC improvement observed in this study were clearly stated in the manuscript:

‘[redacted]’ (academic in confidence). The assessment group was also aware of the observation of a small number of patients who had ‘delayed first efficacy response beyond the 12-week study’ in the sitaxentan STRIDE-1X study. However such phenomenon did not appear to have been observed in subsequent sitaxentan long-term studies. Given these cautions and inconsistencies in available evidence, it was decided after consulting with clinical experts that the assumption that no FC improvement occurs beyond the first cycle of the model is reasonable.