**RESPONSE TO NICE HEALTH TECHNOLOGY APPRAISAL**
**DRUGS FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION**

**Comments relating to technical content of the assessment report**

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1. Comments relating to the methods of assessing clinical effectiveness and cost effectiveness

The systematic review of randomised controlled trials identified in the main trials of short duration where the technologies were added to supportive treatment and compared with supportive treatment alone It was noted that there was a relative lack of trials comparing the technologies against each other, and limited data examining specific types or subcategories of PAH.

1. The report suggests no clinical differences or outcomes between therapies and the economic model as I understand it suggests benefit is equal.

2. Whilst this may be true I do not have the same degree of confidence that we can assume the treatment benefits are equal for the following reasons:

a. The data for Sildenafil used in the report assumes a dose of 20 mg three times a day whilst in the SUPER trial the longer term patients following for a year were titrated up to 80 mg three times a day. The licensing for this drug is at 20 mg three times per day. Moreover the number of class III patients in this study was proportionately low with a larger group of class II

b. As I understand it the mortality data assumes a linear loss of life based on the first 12-16 weeks and moreover that mortality in Class III patients is 5% for each successive 12 weeks without any deterioration to Class IV which is outwith clinical experience.

c. It would appear that the model only allows an improvement in clinical outcome and in particular functional class in the first 12 weeks with no late responses, however, clinical experience suggests that this is not the case and there are data to support this.

d. Functional class as an outcome is flawed for a number of reasons including subjective interpretation before attributing a functional class (particular problem between functional class II and III). From a clinical view point the time to clinical worsening which has been used as secondary end point for a number of randomised controlled trials in PAH is likely to be more reliable and as such carry more clinical weight, after all in practice clinicians use a combination of end points with a view to establishing clinical benefit or worsening to guide therapeutic changes. Moreover functional class changes do not appear to track with either end point such as six minute walking distance.

e. The decision to consider different types of PAH as a common disease process was a pragmatic decision based at the Scoping Meeting given

relatively small numbers of patients within sub-groupings. From a clinical perspective however the disease processes are different and outcomes and responses to treatment do vary.

f. Overall the modelling methodology would appear to rely on potentially incorrect assumptions that are inherent in recycling a 12 week set of data and extending it over a more prolonged period. An example of this relates to assumptions made earlier with regard to mortality from Class III patients.

g. There is relatively little outcome data relating to adverse effects of treatment including drug interactions.

2. Comments on Conclusions:

1. The implications for service provision section, though not explicit, would certainly suggest differential cost effectiveness amongst the oral treatments with Sildenafil taking a lead position. This point may be seized upon by PCTs however, as the report suggests analysis was not designed for comparisons between the technologies and there are concerns relating to methodology as above.

2. The report suggests that Iloprost and epoprostenol may not be cost effective according to NICE guidelines, however, there is overwhelming evidence in support of clinical effectiveness in patients with advanced disease over and above best supportive therapy particularly in patients who are Class IV. Any withdrawal would raise serious ethical concerns were these therapies seriously at risk .

3. The suggested research priorities are an excellent feature of this report and had more data been available then this would have facilitated the technology assessment though this was pointed out at the original scoping meeting. It should be noted however, that the pulmonary hypertensions physicians have submitted evidence based guidelines for the clinical treatment of PAH and have a comprehensive national patient register.

Suggested Modifications to Report:

1. There should be a clear and explicit conclusion that patients with pulmonary arterial hypertension should be managed within the National Designated Centres or their satellite clinics and that all prescribing should take place within these Centres to maximise cost efficacy.

2. There are several summary statements suggesting use of the most cost effective oral treatment could potentially reduce overall treatment costs in the NHS. In practice however, there are many concerns over the methodology on which the statement is based. The concern here of course is the PCTs may focus on this sentence without the accompanying qualifying comments within the broader document.

3. The absence of head to head studies and the concerns over the extrapolation have led the basic modelling to suggest equivalent outcomes in the long term. Hence cost effectiveness seems to be largely based on price and this is potentially erroneous. Until clear evidence arrives all drugs should be available

to be tailored to individual patients needs. This will allow rational decision making for specific disease groups. Examples include patients with pulmonary arterial hypertension associated with connectective tissue disease who also have digital ulcers should receive an endothelin receptor antagonist as first choice and patients with liver disease potentially receive Sildenafil. The side effect profiles, additional clinical benefits, dosing scedules and drug interactions should be highlighted in a clearer fashion.

4. Further modelling based on time to clinical worsening should be considered as this is likely to give a more valid end point for therapeutic success than functional class.

5. There should be a clear statement as to the clinical benefits of prostaglandin therapy in advanced disease

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