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Dear Dr Longson

Health Technology Appraisal – Drugs for the treatment of pulmonary arterial hypertension

The British Society for Rheumatology (BSR) welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal. The comments have been prepared by Professor Chris Denton.

We wish to make a number of points and highlight some specific concerns that relate to patients suffering from autoimmune rheumatic diseases that are unfortunate enough to develop connective tissue disease associated PAH (PAH-CTD). This is a very important group of cases both numerically and medically. For example PAH presently the single most common cause of disease related death in systemic sclerosis (SSc) where up to 10% of cases develop this complication.

- Although there is a convincing body of data, outlined in the appraisal, that confirms clinical responsiveness to licensed therapies in the PAH-CTD subgroup, there is also evidence that this group of PAH has a particularly poor outcome based upon published series (Koh et al 1996 Kawut et al 2006 and Williams et al 2006) and also upon analysis of outcome in the UK national PAH database of cases managed in the PAH centres (Dr Gerry Coghlan, *submitted manuscript enclosed*). Thus we consider that the PAH-CTD subgroup has a particularly high priority for therapy and indeed often benefit from combination therapy (see final bullet point below).

- We routinely use ERA as first line treatment in this group of patients. It is a particular concern that, based upon the economic models applied, sildenafil will be recommended as the initial therapy of choice in all cases of PAH on the basis of apparent economic advantage. Data from controlled trials of patients treated at licensed dose of sildenafil with PAH-CTD arises from only 22 subjects and cannot be regarded as very robust and outcome analysis of the larger group of

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cases treated with higher disease has not yet been publicly released. Conversely, a UK wide registry of CTD PAH has been analysed over the past 5 years, that this confirms the improvement in outcome with ERA treatment seen in extension of RCT's as do data from our own single centre database (Williams et al 2006). Data for the use of endothelin receptor antagonists (ERA) appear to be more positive that those for sildenafil based upon clinical trial data relating to time-to-clinical worsening in the total PAH population. It would not be consistent with current practice if all PAH-CTD cases in functional class III were started on sildenafil monotherapy.

- The synthesis of data relating to time to clinical worsening causes significant concern as I believe that analysis of time to clinical worsening in the clinical section of the appraisal is flawed. In the bosentan section, BREATHE-1 and the 351 trial (Channick et al) show favourable effects alone or combined on time to clinical worsening. Only by adding the open label portion of STRIDE-2 can they suggest that such an effect does not reach significance. This is a highly prejudicial assessment, first open label data are being combined with placebo controlled data. Second it ignores the bias inherent in the STRIDE 2x trial. Patients on sitaxentan that were thought to have deteriorated went to commercial treatment, while those on bosentan could enter the STRIDE-3x trial. I believe that this made investigators more likely to change from bosentan that from sitaxentan. Including these data and ignoring what had been shown in DBRCTs is unacceptable.

- There are some ways in which the long term costs are determined that may be misleading. The assumption that mortality in class 3 is 5% per 12 weeks is flawed. In practice these patients will usually progress to class 4 and have additional costs due to epoprostenol exposure. Any improvement occurring at later stages of disease after initiation of therapy would have a significant impact on total treatment cost for patients. In clinical practice it is not uncommon in the case of ERA to see improvement in functional class more than 12 weeks after initiation of therapy. This is not incorporated into the cost model.

- Data do not support the assumption that the rate of deterioration for any given functional class is the same. For sildenafil and sitaxentan data from a DBRCT do not support this. Recent data from a national registry data provide real-life information concerning the treatment of the PAH-CTD population in UK (*manuscript enclosed*). We consider that these data suggest that [redacted]. As outlined above, we consider that ERA remain the therapy with proven first line impact in this population, and request that as combination therapy is not economically disadvantageous when compared to

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prostanoid therapy that the door not be shut on this option especially in this group where the registry data is supportive pending confirmation in RCTs.

In conclusion the BSR feels strongly that this technology review may be open to misinterpretation. The particularly challenging group of PAH-CTD would be seriously disadvantaged if sildenafil at current licensed dose becomes standard first line treatment. This does not reflect clinical practice in centres that are successfully managing CTD-PAH with improved survival using ERA as first line therapy and moving to combination therapy when clinically indicated.

Yours sincerely,

[redacted]

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