NICE Review of Therapies for Pulmonary Arterial Hypertension

Reply from Actelion Pharmaceuticals UK – 25th September 2007

1. Summary

1.1 The Assessment Report (AR) summary indicates that the three oral therapies may be cost-effective. However, it also states (AR, pg 29) that '..*The findings…. suggest the possibility of differential cost-effectiveness between the oral treatments. This requires further confirmation as current analysis was not designed for direct comparison. If confirmed, the most cost-effective treatment would result in cost-savings for the NHS'.* If the results in the report are compared, the most cost-effective treatment would be deemed to be sildenafil.

1.2 We agree that bosentan is cost-effective, but we strongly disagree with the inference regarding sildenafil.

1.3 We believe that NICE, as an evidence driven organisation, will find it difficult to support the approach taken by the AG towards sildenafil data. Equal weight has been given to the sildenafil database comprising only 40 patients treated in-licence, at 20 mg tds for 12 weeks, compared to the bosentan database of 4 RCTs, over 180, in-licence patients and follow-up in some cases to 3 yrs

1.4 We would argue that the use of NYHA functional class (FC) transitions as the base of the economic model introduces a significant degree of uncertainty. Time to Clinical Worsening (TTCW) (death, transplantation, hospitalization for PAH or escalation of PH treatment), a measure of morbidity & mortality as used in the pivotal studies for the oral products, would have been a more appropriate choice.

1.5 Since the AG model was developed based on the minimum dataset common to all comparators, the results derived cannot be interpreted without careful consideration of the assumptions and a cross-validation versus additional existing evidence

1.6 Had sildenafil been reviewed as a Single Technology Assessment (STA), it seems likely that a conclusion of 'not proven' would have been drawn, on the basis of the limited dataset and the subsequent uncertainties associated with the economic model. On that basis, it follows that a similar conclusion would hold valid in this multiple technology assessment.

2. Economic Model

2.1 The treatment of PAH is complex and it is clearly a challenge to develop an economic model which can be applied to the different therapies whilst still addressing the complexities of the disease. As a pragmatic solution, the model adopted reflects a simplified treatment algorithm. This simplification is reliant upon the lowest common denominator across the datasets submitted. Consequently, much of the detail within the more complete data sets submitted has not been fully utilised. This solution thus excludes most of the strong, differentiating, data provided for bosentan.

2.2 The two variables driving the model results are NYHA (FC) transitions and mortality. The major areas of concern are described below.

NYHA Functional Class (FC) Movement

2.2.1 The measurement of FC and therefore FC movement is highly subjective and crude as described by Hoeper at al[1], and within the Actelion submission to NICE (Pg 13). FC is a measure of physical functioning, e.g. how breathless a patient is in performing general physical activities at a given point in time. It does not necessarily reflect the progress of the underlying disease. Sensitivity is also limited, as there can be significant improvements and deteriorations *within* a class, in particular FC III. It is thus not uncommon for physicians to use the term FC 'IIIa' or 'IIIb' to describe their patient's status. As a consequence, FC transitions are usually secondary, or in the case of the sildenafil pivotal study, tertiary end-points in clinical trials. It is inappropriate to use such a subjective and insensitive end-point as a key clinical parameter in the economic model.

2.2.2 Data on FC shifts has been gathered from the pivotal trials, but is particularly limited in the case of sildenafil. At the licensed dose of 20 mg tds there is efficacy data only from one, 12 week study. (AR, pg 140). Within this study there were only 40 FC III patients treated at this dose. In the economic model these results are the sole source for FC shifts for patients treated with sildenafil. This is not robust and the uncertainty around the results is clearly high.

2.2.3 The model then assumes that FC improvements at 12/16 weeks in the clinical trials, are a 'one time event', while FC deteriorations are representative of changes up to 30 years and repeat every 12 week cycle. These assumptions and extrapolation of short-term data introduce error:

- The Sitbon et al 2007 data (unpublished, Actelion submission ref 31) demonstrate that patients receiving bosentan [redacted]. The Sitbon et al report, together with the raw data, were provided but were not used by the AG.
- In addition, Sheldon[2] commented over a decade ago on the limitation of extrapolating short term data in economic models.

2.2.4 The importance of the FC transition variable, and the potential uncertainty in the decision over the most cost-effective intervention, can be highlighted by AR Figures 45 and 65, (attached). These figures demonstrate the large variations in results associated with bosentan and sildenafil, when varying the transition probabilities of progressing from FCIII to FCIV. Bosentan would be the most cost-effective intervention on approximately 20% of simulation runs, even with the limitations in the model. This value of 20% would increase if the model were calibrated to be consistent with the lack of significant improvement in 'time to clinical worsening' (TTCW, see section 3.4) associated with sildenafil and sitaxentan i.e. these therapies have no proven benefit on TTCW and thus would be expected to show a faster rate of movement into FC IV (an 'expensive state') over time, in comparison to bosentan.

2.2.5 Using a TTCW approach sildenafil is extremely unlikely to be cost-effective, given that it produces a non-significant effect on TTCW as reported in SUPER-1[3]. This implies that

[1] Hoeper et al. Trial Designs in PAH. JACC 2004;43(12) Suppl S:48S-55S.
[2] Sheldon TA, "Problems in using modelling in the economic evaluation of health care" Health Econ. 5(1):1-11
[3] Galie N et al. Sildenafil citrate therapy for pulmonary arterial hypertension. NEJM 2005;353:2148-2157

patients on sildenafil would reach epoprostenol treatment at the same time as patients who are on supportive care, as the use of additional PAH medication was explicitly incorporated in the TTCW definition. Using such an assumption would result in approximately equal costs of care, excluding drug costs, for both supportive care and sildenafil. We would expect minor gains in QALY for patients on sildenafil that would be associated with the temporary improvement in functional class that was shown in Super 1 on initiation of treatment. This improvement is unlikely to be maintained due to the non-significant effect on TTCW. Given that sildenafil costs £4,000 per annum, a year on year utility gain of over 0.1 per patient would be required for sildenafil to be approaching a cost per QALY value of £30,000. This situation is very unlikely to be achieved, as it is the equivalent of all patients being one FC less severe than patients on supportive care, *despite* no significant benefit in TTCW.

General Model Validity and Interpretation

2.2.6 There is a discrepancy between the results predicted by the model and the known data. Within the Assessment Group model there are large differences between active treatment and supportive care in the proportion of patients who progress to FC IV, a highly significant cost driver within the model and a reflection of 'clinical worsening'. After 2 years it is expected that approximately 30% of patients who began on supportive therapy would be in FC IV. For bosentan this value would be approximately 10%. As the assumed mortality rates and the number of QALYs generated within the AG model are relatively similar for bosentan and sildenafil, we have inferred that the transition probabilities must also be similar. Were this correct we must estimate similar results to bosentan i.e. approximately 10% of patients on sildenafil would be in FC IV after 2 years, compared with approximately 30% for supportive care alone, *despite* there being no positive impact of sildenafil on TTCW as described in AR Table 29. By contrast, bosentan has a significant effect on time to clinical worsening in the 2 pivotal trials.

2.2.7 It is noted that interventions without mortality benefit will appear more cost-effective, as a consequence of the fact that patients will die sooner within FC III and thus avoid the 'costly transition' into FC IV. Care is therefore required in interpreting the cost-effectiveness results

2.2.8 In summary, results from the AG model must be interpreted with care, and validated in light of the clinical evidence.

3. Clinical Evidence

Underlying Aetiology

The AG has not differentiated between therapies in its recommendations and we question the appropriateness of this approach.

3.1 Bosentan is the only therapy within the NICE review for which significant results have been described in multiple, aetiology specific, patient groups. These studies have demonstrated consistent effects of bosentan on both short and in some cases long-term end-points in PAH related to connective tissue disease (CTD) and congenital heart defects (CHD), in addition to idiopathic PAH.

3.2 Although the clinical symptoms of PAH are generally similar regardless of the under-lying cause, important differences exist at the physiological level. It should not be assumed that efficacy demonstrated in idiopathic PAH (iPAH) is transferable to another aetiology.

3.3 SUPER-1[3], the only sildenafil study presenting results on the licensed dose, included only 4 and 19 patients at 20 mg tds, with PAH related to CHD and CTD respectively (of whom an estimated

60% would be in FC III). This is insufficient data on which to draw a robust conclusion regarding efficacy in these sub-groups of PAH patients. It would therefore be unreasonable to propose that these patient groups receive sildenafil as first-line oral treatment.

Functional Class, limitations to the reliance on this as an end-point have been described in Section 2.2.

Time to Clinical Worsening (TTCW).

3.4 Time to clinical worsening (death, transplantation, hospitalization for PAH or escalation of PH treatment) is a composite endpoint reflecting morbidity & mortality. The individual measurements are objective. This is a more appropriate end-point than FC shifts with which to reflect clinical deterioration in an economic model. While TTCW was included in the pivotal trials for the 3 oral therapies, only bosentan demonstrated a statistically significant, placebo corrected effect. This result was reproduced in the 2 registration trials [4,5] and further supported in the more recent study in patients with PAH related to CHD [6]

3.5 As outlined in section 2.2.7, since sitaxentan and sildenafil have consistently failed to demonstrate a statistically significant effect on TTCW, a contradiction exists in the current model, where all products are given similar functional class and observed mortality benefit, implying similar impact on the rate of clinical worsening.

Observed Mortality Data.

Observational, long-term follow up data is available for a number of products. However, within the economic model these data have been given equal weighting whereas it is surely reasonable to expect that any major variations between data sets would be fully reflected in the model.

3.6 Within the follow-up of the pivotal sitaxentan trial, STRIDE –2, a 1 yr mortality rate of 95% is described, However, at baseline these patients constituted a mixed population with 33% FC II (ie less severe) and 66% FC III patients, of whom 24% were receiving different or additional treatment at the 1 yr point. (ref, SmPC). The bosentan data[7,8] described a similar death rate, but based on a pure FC III population at baseline, and within which only 11% required additional or different therapy at 1 yr. This significantly differentiates these products within the broad class of endothelin receptor antagonists.

3.7 There is no long-term data available on sildenafil 20 mg tds and thus no evidence of a mortality benefit at this dose (AR, Pgs 139-148). This is also stated in the SmPC. Twelve month mortality data is only available at 80 mg tds, a dose specifically not approved by the EMEA. In making an estimate of cost-effectiveness via an economic model, the Assessment Group has subscribed a mortality benefit to sildenafil (Table 44, Appendix 9). This assumption is not justified.

Sildenafil in Clinical Practice

3.8 The impact of any recommendation from NICE must be considered in relation to their expected impact normal clinical practice. Bosentan and sildenafil have been available to physicians for many years, and Actelion's research indicates that the majority of newly diagnosed FC III PAH

[4] Channick R et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo controlled study. Lancet 2001;358:1119-1123
[5] Rubin L et al. Bosentan therapy for pulmonary arterial hypertension. NEJM 2002;346(12):896-903
[6] Gaile N et al. Bosentan improves hemodynamics and delays time to clinical worsening in patients with mildly symptomatic PAH: results of the EARLY study. ESC 2007 [Abstract 1011]
[7] Mclaughlin VV et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. Eur Resp J 2005;25:244-249
[8] Sitbon O et al. Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first line bosentan compared with an historic cohort treated with i.v. epoprostenol. Thorax 2005:60;1025-30

patients on a targeted therapy receive bosentan as their first drug, while sildenafil is more commonly given in combination.

3.9 When given as monotherapy, for clinical reasons sildenafil is frequently titrated up to doses beyond 20 mg tds, mostly to 50 mg tds but sometimes as high as 100 mg tds. Most of the studies described in the AR (AR,Pg 140) reflect the use of sildenafil above the licensed dose. This fact may indicate why there is limited data on the licensed dose of 20mg tds. It also has a cost, and therefore a cost-effectiveness, implication.

4. Conclusion

4.1 Bosentan is the only therapy consistently demonstrated to be effective. This can be shown across both short and long-term studies, on multiple clinical end-points including TTCW and in multiple aetiologies of PAH

4.2 The Assessment Group economic model has significant limitations, in particular in relation to the use of functional class transitions as a key input parameter. Whilst a FC model may provide a reasonable approximation of cost-effectiveness, for interventions with proven benefit on TTCW the favourable bias associated with treatments that have no such proven effect, is likely to be large, rendering these results as extremely uncertain.

4.3 The sildenafil dataset of 40 'in-license' patients is limited. No meaningful conclusion can be drawn with regard to cost-effectiveness. We would argue therefore that 'not proven" is the only justifiable outcome for this product, if evidence based criteria are used to support decision making.

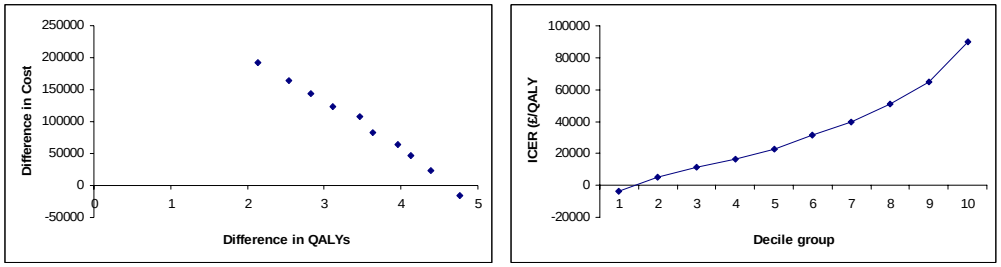

Figure 45 in AR- Bosentan variation by odds ratio of deterioration from III to IV after first cycle

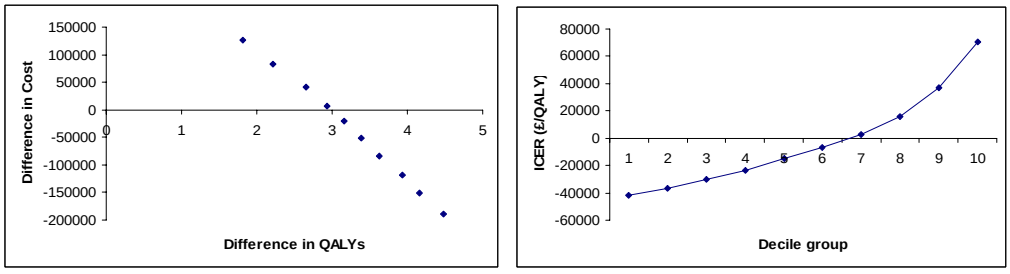

Figure 65 in AR - Sildenafil variation by odds ratio of deterioration from III to IV after first cycle