Epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for the treatment of pulmonary arterial hypertension in adults

Committee meeting – 5 February 2008

Results of the request for additional survival data and incremental results of cost-effectiveness analysis

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Section 1: request for additional data on survival

Background

At the Appraisal Committee meeting on 3 October 2007, it was agreed that the Committee should request from consultees and commentators additional survival data on pulmonary arterial hypertension (PAH). The Committee wanted to compare the further data received with the Assessment Group's (AG) survival rate assumptions.

In appendix 9 of the AG report (page 293), the following survival rates were assumed:

- epoprostenol in functional class (FC) IV over a 3-year period has a survival rate of 0.47 (0.39–0.55)
- epoprostenol and iloprost in FC III over a 3-year period have a survival rate of 0.75 (0.71–0.79)
- bosentan in FC III over a 3-year period has a survival rate of 0.87 (0.81–0.92)
- sitaxentan and sildenafil in FC III over a 1-year period have a survival rate of 0.95 (0.90–0.98).

Total number of submissions: **four**

Summary of submissions

1. Actelion

Actelion, the manufacturer of bosentan, provided an Excel spreadsheet of 235 patients who had idiopathic PAH (iPAH) and connective tissue disease (CTD). This spreadsheet originally accompanied Actelion's submission and was sent to the AG. Although the spreadsheet contained details of the patients and how long they had been on bosentan, there was no analysis of the survival rate.

2. Encysive

Encysive, the manufacturer of sitaxentan, provided a Kaplan-Meier (K-M) estimate of time to death, including follow-up, with subjects on the licensed dose of 100 mg. These data were provided from a pooled analysis of the STRIDE-2 trial and the STRIDE-2 extension trial. These trials were included within the AG report. They provide the K-M rate point estimates at 1 and 2 years for 145 patients. The first year cut-off K-M rate of [redacted]. The second year cut-off K-M rate of [redacted].

3. National Pulmonary Vascular Diseases Unit

The National Pulmonary Vascular Diseases Unit (NPVDU) made two submissions, the first an unpublished manuscript entitled 'Connective tissue disease associated pulmonary arterial hypertension in the modern treatment era: the United Kingdom experience'. This document provided details on [redacted]. The only mention of survival rates in relation to the drugs under appraisal was by reference to a paper by Sitbon O, Humbert M, Nunes H et al. (2002) on the use of epoprostenol in PAH. This paper was included in the AG report and states that for 178 patients with iPAH who were treated with epoprostenol the 1- and 3-year survival rates were 85% and 63% respectively.[1]

[1] Sitbon O, Humbert M, Nunes H et al. (2002) Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. Journal of the American College of Cardiology 40(4): 780–8.

The second submission by the NPVDU was a report on a survey conducted in six of the seven designated UK centres on survival with iPAH. A summary of the survey results follows in tables 1.1–1.6.

Survey summary

- Total number of patients with iPAH = [redacted].
- Median age of first treatment = [redacted].
- Mean survival = [redacted].

Table 1.1 Average survival of all patients

	Year 1	Year 2	Year 3
Average survival	[redacted]	[redacted]	[redacted]
Number of cases remaining	[redacted]	[redacted]	[redacted]

Table 1.2 Average survival by gender

* 1 unidentified	Number	Survival at year 1	Survival at year 2
Males	[redacted]	[redacted]	[redacted]
Females	[redacted]	[redacted]	[redacted]

Table 1.3 Distribution of FC within the survey

	Total
Class I	[redacted]
Class II	[redacted]
Class III	[redacted]
Class IV	[redacted]
Unidentified	[redacted]
Total	[redacted]

Table 1.4 Survival rate by FC

	Survival at year 1	Survival at year 2
FC III	[redacted]	[redacted]
FC IV	[redacted]	[redacted]

Table 1.5 First-line drug therapies

First-line drug treatment	Number of patients
Bosentan	[redacted]
Sildenafil	[redacted]
Sitaxentan	[redacted]
Ambrisentan	[redacted]
IV prostanoids (epoprostenol and a few iloprost)	[redacted]
Sub-cut prostanoids (treprostanil)	[redacted]
Inhaled prostanoids (iloprost)	[redacted]
Total	[redacted]

It is noted in the NVPDU report that, in general,

[redacted].

Table 1.6 gives survival rates stratified by class of drug (oral therapies vs prostanoids) after one and two years. The survival rate of those on prostanoids combines both FC III and IV. The survival rates are [redacted] (both for those on oral therapies and those on prostanoids) than the AG's assumptions.

Table 1.6 1- and 2-year survival

Therapy	Number initiated on therapy	Year 1 survival	Year 2 survival
Oral	[redacted]	[redacted]	[redacted]
Prostanoids	[redacted]	[redacted]	[redacted]

[redacted] The survival rates for people taking sildenafil in year 1 are [redacted] assumed by the AG, and they also show [redacted] in year 2. The survival rates for bosentan are [redacted] than those estimated by the AG. The survival rates assumed for bosentan in the cost-effectiveness analysis were derived from clinical trials, which may include patients with different characteristics from the real-life setting illustrated by this survey.

Table 1.7 Sildenafil and bosentan survival rates

Therapy	Number initiated on therapy	Year 1 survival	Year 2 survival
Sildenafil	[redacted]	[redacted]	[redacted]
Bosentan	[redacted]	[redacted]	[redacted]

It is noted in the report that [redacted] and that many who

were initiated on sildenafil were entered as part of the SUPER trial (AG report, page 139). Also,

(confirmed by three centres). The report concludes the following on sildenafil:

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4. West Midlands Specialised Services Agency

The West Midlands Specialist Services Agency (WMSSA) made two submissions. The first is a forecasting report from the third quarter of the financial year 2006/07.

[redacted].

Section 2: incremental results of cost-effectiveness analysis

The AG found that the oral drugs (sildenafil, sitaxenten and bosentan) in the reference case had incremental cost-effectiveness ratios (ICERs) relative to supportive care that were all below £30,000.

At the Appraisal Committee meeting, the Committee requested that these results be presented as an incremental analysis comparing all the drugs with each other and supportive care. The resulting ICERs are shown in Table 2.1 below.

Table 2.1 Incremental cost-effectiveness of oral treatments and supportive care

Strategy	Cost (£)	Quality-adjusted life years (QALYs)	ICER (£/QALY)
Sildenafil	307,000	5.436	–
Supportive care	343,000	2.201	Dominated
Sitaxentan	419,000	5.289	Dominated
Bosentan	436,000	5.696	496,000

Given that the prostanoids (epoprostenol and iloprost) are used in different (generally more severely ill) groups of patients, it was not appropriate to include them in the above analysis.