Pixantrone monotherapy for treating relapsed or refractory aggressive non-Hodgkin's lymphoma

ERG's critique of CTI Life Sciences' revised patient access scheme submission

BMJ Technology Assessment Group

Evidence Review Group critique of CTI Life Sciences' revised patient access scheme submission for pixantrone monotherapy for treating relapsed or refractory aggressive non-Hodgkin's lymphoma

Produced by	BMJ-Technology Assessment Group (BMJ-TAG)
Date produced	08/11/2013
Authors	Steve Edwards, Head of BMJ-TAG, London Samantha Barton, Senior Health Technology Assessment Analyst, BMJ-TAG, London Nicola Trevor, Health Economics Lead, BMJ-TAG, London Fatima Salih, Health Economist, BMJ-TAG, London
Correspondence to	Dr Steve Edwards, Head of BMJ-TAG, BMA House, Tavistock Square, London, WC1H 9JP.

CTI Life Sciences has submitted a financially based revised patient access scheme (PAS), outlined in the document forwarded to the National for Health and Care Excellence (NICE) dated 05/11/13. The PAS constitutes a [redacted] discount on the UK list price of pixantrone.

In summary, the Evidence Review Group (ERG) considers the key point to be the substantial amount of uncertainty associated with the clinical and cost-effectiveness of pixantrone in the population of patients that is the focus of the manufacturer's revised PAS submission.

The ERG notes that, in Section 3.4 the manufacturer indicates that the revised PAS would apply to patients with aggressive B-cell non-Hodgkin's lymphoma (NHL) who:

- have disease confirmed by **central** independent pathological evaluation (rather than **onsite** pathological evaluation) and;
- have received 2 or 3 lines of prior treatment and;
- have previously received rituximab.

The ERG agrees that this subgroup of NHL patients is most characteristic of UK patients likely to be eligible for treatment with pixantrone.

In Section 3.14, the manufacturer refers to comparative clinical effectiveness data for pixantrone versus treatment of physician's choice (TPC) provided in the manufacturer's response to the first Appraisal Consultation Document (ACD), dated 02/05/2013 (re-presented in Appendix 1 of the revised PAS submission). The ERG can confirm that these data are consistent with the data for this population originally submitted in the manufacturer's response to NICE clarification questions.

Also in Section 3.14, the manufacturer highlights that the model upon which the cost-effectiveness results are based includes no further amendments (other than the revised PAS) compared with the model submitted to support the manufacturer's original PAS, dated 26/07/13. The ERG carried out the following cross checks of consistency between the current and previous version of the manufacturer's PAS model:

1. PAS discount was set to 0 and consistency between incremental cost-effectiveness ratios (ICERs) was examined;

2. Individual costs for adverse events were checked against those previously used;

3. The manufacturer's original PAS model was re-checked for consistency with the model submitted (dated 01/05/13) in response to the ERG comments on the manufacturer's response to the first ACD.

The ERG can confirm that only the price of pixantrone differs between the current version of the manufacturer's model and that used in the previous PAS submission, dated 26/07/13.

Furthermore, the ERG carried out validation of the manufacturer's revised base case cost-effectiveness and sensitivity analysis results. No errors were identified; however, the ERG notes that some of the results (presented in Table 1) are unexpected, for example, the use of the upper 95% confidence interval (CI) of the parameters used to estimate overall survival (OS) with pixantrone (i.e., increasing the OS associated with pixantrone), results in an increase in the ICER. Similarly, use of the lower 95% CI of the parameters used to estimate OS with TPC (i.e., decreasing the OS associated with TPC) results in a higher ICER. However, following examination of the incremental costs and incremental quality adjusted life years (QALYs) associated with each analysis, the ERG considers the manufacturer's analyses to be correct and notes that improvement in the relative survival of patients treated with pixantrone versus TPC, results in an increased gain in QALYs that is associated with an increased gain in costs.

Table 1. Parameters varied and results of manufacturer's deterministic sensitivity analysis - with PAS [redacted] discount (adapted from Table 10, manufacturer's revised PAS submission)

Parameter	Baseline value	Alternate value(s)	Incremental costs	Incremental QALYs	Reported in written submission ICER* (INB)
All parameters at baseline values			[redacted]	0.20	£18,462 (£ 2,336)
Progression free survival: Pixantrone	Mean	97.5% Upper	[redacted]	0.23	Dominant (£ 11,575)
		2.5% Lower	[redacted]	0.16	£ 116,119 (-£ 13,733)
Progression free survival: TPC	Mean	97.5% Upper	[redacted]	0.17	£ 82,152 (-£ 9,083)
		2.5% Lower	[redacted]	0.21	Dominant (£ 6,597)
Overall survival: Pixantrone	Mean	97.5% Upper	[redacted]	1.21	£ 54,074 (-£ 29,205)
		2.5% Lower	[redacted]	-0.31	Less costly and less effective £ 43,464(£ 4,180)
Overall survival: TPC	Mean	97.5% Upper	[redacted]	-0.79	Less costly and less effective £ 72,200 (£ 33,338)
		2.5% Lower	[redacted]	0.62	£ 46,579 (-£ 10,344)

*Cost per QALY.

Abbreviations used in table: ICER, incremental cost-effectiveness ratio; INB, incremental net benefit; QALY, quality adjusted life year; TPC, treatment of physician's choice.

The manufacturer's probabilistic sensitivity analysis was carried out across 5,000 simulations and resulted in an average ICER (mean incremental costs/mean incremental QALYs) of £22,024 per QALY (with revised PAS). The scatter plot of cost-effectiveness results (with revised PAS) and cost-effectiveness acceptability curves (with revised PAS) are displayed in Figures 1 and 2, respectively. According to the manufacturer's probabilistic analysis, pixantrone (with revised PAS) was associated with a 49.3% and 55.7% probability of being cost-effective versus TPC at willingness-to-pay thresholds of £20,000 and £30,000, respectively. The percentage of probabilistic simulations (with revised PAS) falling in each quadrant of the cost-effectiveness plane is summarised in Table 2. The ERG considers it important to note that, although 68% of probabilistic iterations estimated that pixantrone was associated with greater benefit than TPC, 32% of probabilistic iterations indicated that patients treated with pixantrone fared worse than those treated with TPC.

Figure 1. Scatter plot of probabilistic cost-effectiveness results of pixantrone (with revised PAS) compared with treatment of physician's choice (adapted from manufacturer's revised PAS submission, Figure 5, pg 27)

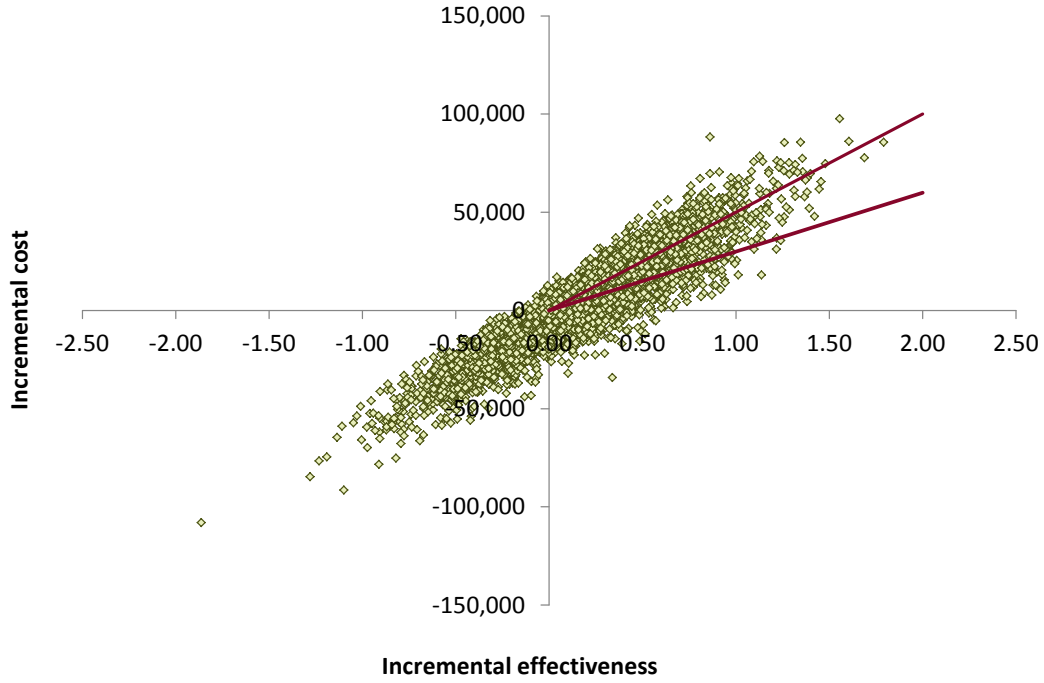

Figure 2. Cost-effectiveness acceptability curves for pixantrone (with revised PAS) and treatment of physician's choice (adapted from manufacturer's revised PAS submission, Figure 6, pg 28)

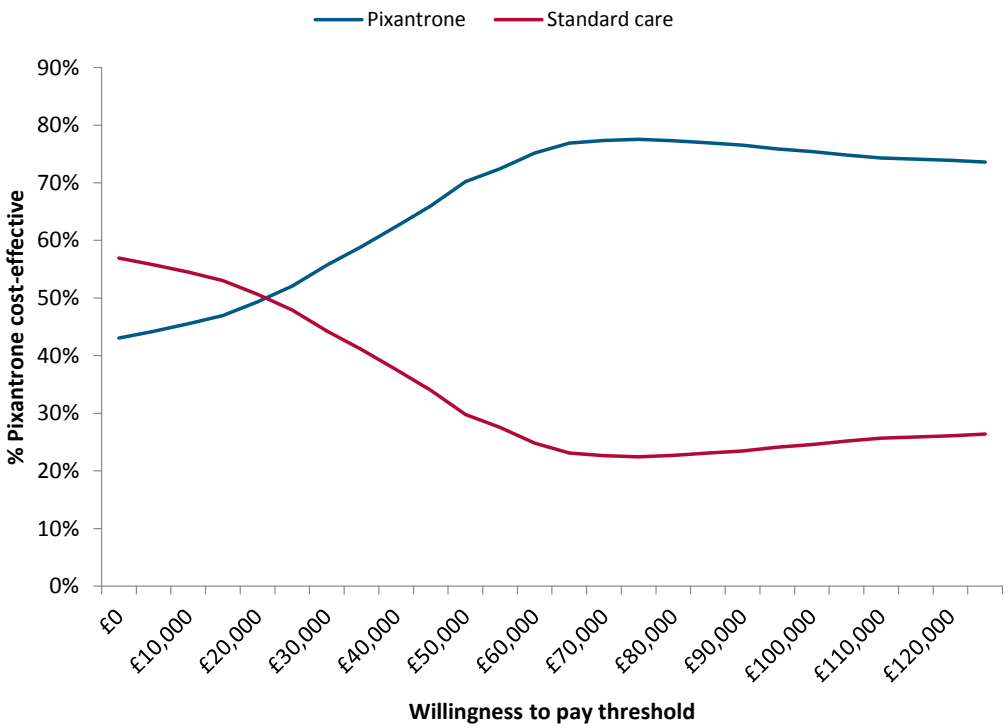

Table 2. Percentage of probabilistic simulations (pixantrone [with revised PAS] vs TPC) falling in each quadrant of the cost-effectiveness plane (reproduced from manufacturer's revised PAS submission, Table 12, pg 28)

Quadrant	Percentage of iterations
Quadrant I – Pixantrone has higher costs and higher effectiveness	55%
Quadrant III – Pixantrone has lower costs and lower effectiveness	31%
Quadrant IV – Pixantrone is dominant (i.e. has lower costs and higher effectiveness)	13%
Quadrant II – Pixantrone is dominated (i.e. has higher costs and lower effectiveness)	1%
Abbreviations used in table: PAS, patient access scheme; TPC, treatment of physician's choice.	