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

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

BMJ Technology Assessment Group

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

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CTI Life Sciences has submitted a financially based patient access scheme (PAS), outlined in the document forwarded to the National for Health and Care Excellence (NICE) dated 25/07/13. The PAS constitutes a [redacted] discount on the UK list price of pixantrone.

In summary, the Evidence Review Group (ERG) considers the key points to be:

- Based on the licensed indication and UK clinical practice, the ERG considers it important to evaluate patients with retrospective (**central**) histological confirmation of aggressive B-cell non-Hodgkin's lymphoma (NHL) and who have previously received treatment with rituximab. The ERG considers it appropriate to evaluate patients receiving pixantrone as a third or fourth line treatment as a subgroup;
- As a result of the small sample size available in the patient population that is the focus of the manufacturer's PAS submission, clinical and cost-effectiveness results are associated with substantial uncertainty.

In Section 3.4 of the submission, the manufacturer indicates that the PAS would apply to patients with aggressive B-cell 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 their response to the Appraisal Consultation Document (ACD) for the subgroup of patients with **central** histological confirmation of disease, receiving pixantrone as a third or fourth line treatment, and who had previously received rituximab (CTI ACD response, Table 5, pg 14). As noted by the ERG in its assessment of the manufacturer's response to the ACD, data provided by the manufacturer in response to the ACD differ from those provided for the same subgroup of patients as part of the clarification process. As recorded in the withdrawn FAD, originally released after the second Appraisal Committee meeting on 15/05/13, the manufacturer acknowledged that Table 5 of the ACD response was erroneously labelled and that data were from a population of patients with aggressive B-cell NHL, confirmed by **onsite** pathological review. The difference in the number of patients in each subgroup could be considered minimal. However, there is a substantial disparity in the gain in median overall survival (OS) associated with pixantrone, with data provided in response to the ACD suggesting that pixantrone prolongs median OS by 4.1 months compared with 2.9 months based on data provided during clarification. It should be

noted that the difference between the treatment groups in median OS does not reach statistical significance in either analysis.

Clinical effectiveness data for the subgroups of patients provided by the manufacturer in response to the ACD and during clarification process are summarised in Table 1.

The ERG considers it important to reiterate the considerable uncertainty around the clinical effectiveness of pixantrone in this population.

Table 1. Clinical effectiveness for subgroup analyses based on line of therapy in patients with histologically confirmed aggressive B-cell NHL, receiving pixantrone as a third or fourth line treatment, who had previously received rituximab

	Onsite histological confirmation (from ACD response)			**Central histological confirmation (from manufacturer's clarification response)**		
Outcome	**Pixantrone (N = 25)**	**TPC (N = 25)**	**Measure of effect (p value or HR with 95% CI)**	**Pixantrone (N = 20)**	**TPC (N = 18)**	**Measure of effect (p value or HR with 95% CI)**
CR/CRu (end of study)	6 (24%)	1 (4%)	Reported as not significant	5 (25.0%)	1 (5.6%)	0.184
CR (end of study)	5 (20%)	0	p <0.05	5 (25.0%)	0 (0%)	0.048
ORR (end of study)[a]	11	3	Reported as not significant	9 (45.0%)	2 (11.1%)	0.033
Median PFS, months	4.3	2.8	0.83 (0.46 to 1.50)	5.4 (0.7 to 24.0)	2.8 (0.0 to 10.3)	0.52 (0.26 to 1.04)
Mean PFS (SD), months	–	–	–	6.4 (6.19)	3.2 (2.71)	–
Median OS, months	10.2	6.1	0.90 (0.47 to 1.75)	7.5 (1.1 to 24.0)	5.4 (0.2 to 22.5)	0.76 (0.38 to 1.55)
Mean OS (SD), months	–	–	–	9.9 (8.15)	7.9 (7.85)	–

[a] Includes patients with a partial response.

Abbreviations used in table: ACD, Appraisal Consultation Document; CR, complete response, CRu, unconfirmed complete response; HR, hazard ratio; NHL, non-Hodgkin's lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SD, standard deviation; TPC, treatment of physician's choice.

As requested in Section 3.15 of the NICE PAS submission template, the manufacturer submitted an updated economic model; containing the PAS and aligned with the assumptions that the Appraisal Committee considered to be most plausible. Following the second Appraisal Committee meeting:

> 4.14 "the Committee concluded that the subgroup with aggressive B cell lymphoma confirmed by **central** independent pathological review for third- or fourth-line treatment and who had previously received rituximab was the most likely to represent the population who would be treated with pixantrone in clinical practice. Therefore, the Committee concluded that this was the most appropriate population for decision-making and that it should inform the cost-effectiveness analyses";
>
> 4.15 "The Committee agreed that the manufacturer's utility values used in the original economic model (0.81 for the pre-progression health state and 0.60 for the post-progression health state) were likely to overestimate the quality of life for patients receiving third- or fourth-line treatment for relapsed or refractory aggressive non-Hodgkin's lymphoma. Conversely, it decided that the ERG's utility values (0.428 for the pre-progression health state and 0.279 for the post-progression health state) were likely to underestimate the quality of life for this population";
>
> 4.15 "The Committee concluded that, because of the utility values used, the manufacturer's revised model was still likely to produce ICERs that were lower than the true values";
>
> 4.4 "The Committee concluded that these fundamental concerns about the design of PIX301 meant that there was considerable uncertainty in the validity and robustness of its results".

As highlighted above, the ERG considers the patient population that is the focus of the manufacturer's PAS submission to be the most characteristic of UK patients likely to be eligible for treatment with pixantrone. The ERG notes that at the second Appraisal Committee meeting the manufacturer confirmed that data from the population of patients confirmed by **central** independent pathological review were used to inform the revised model (submitted in response to the ACD). Furthermore, the ERG notes that the same clinical data are used to inform the manufacturer's revised model and PAS model. However, as highlighted above, the ERG considers it important to reiterate the considerable uncertainty around the clinical effectiveness of pixantrone in the patient population that is the focus of the manufacturer's PAS submission.

In addition, the ERG notes that in the revised model submitted in response to the ACD and in the model submitted alongside the current PAS, the manufacturer has used health state utility values from renal cell carcinoma patients receiving second-line treatment. Furthermore, the ERG notes that these utility values, whilst less favourable than those used in the manufacturer's original submission and more favourable than those used in the ERG's sensitivity analysis, may still overestimate the utility of third or fourth line aggressive B-cell NHL patients.

In addition to the PAS and use of assumptions deemed most plausible by the Appraisal Committee, in the updated model the manufacturer has modified the costs associated with drugs (other than

pixantrone) and adverse events. These revisions were based on ERG feedback on CTI Life Sciences' comments on the ACD; dated 10/05/13. The ERG validated the cost inputs used in the manufacturer's updated model versus those presented by the ERG in response to CTI Life Sciences' response to the ACD and identified no errors. Based on the manufacturer's updated model, the incremental cost-effectiveness ratio (ICER) of pixantrone versus TPC is £23,796 per quality adjusted life year (QALY) and £46,654 per QALY with and without the PAS, respectively. Table 2 summarises the base case incremental analysis of pixantrone versus TPC with and without application of the manufacturer's PAS.

Table 2. Base case incremental results with and without PAS (adapted from manufacturer's PAS submission, Tables 8 and 9, pg 20)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Without PAS							
TPC	£38,606	0.94	0.66	-	-	-	-
Pixantrone	£48,054	1.17	0.87	£9,448	0.23	0.20	£46,654
With PAS							
TPC	£38,606	0.94	0.66	-	-	-	-
Pixantrone	[redacted]	1.17	0.87	[redacted]	0.23	0.20	£23,796
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality adjusted life year; TPC, treatment of physician's choice.							

Sensitivity analyses

As per the manufacturer's original submission, deterministic and probabilistic sensitivity analyses were carried out by the manufacturer on the updated model base case. Deterministic sensitivity analysis revealed that the manufacturer's updated model was most sensitive to the parameters and/or distribution used to inform estimates of OS. For example, using the lower 95% CI of parameters used to inform OS with pixantrone increased the ICER (with PAS) to £54,961 and using the generalised Gamma rather than log-normal distributions to inform estimates of OS (and progression free survival) resulted in a deterministic ICER (with PAS) of £2,739 (pixantrone vs TPC). The ERG considers that this reflects the high level of uncertainty surrounding estimates of clinical effectiveness which results from the small sample size available in the patient population that is the focus of the manufacturer's PAS submission.

Furthermore, the ERG notes that the absence of utility data in the relapsed or refractory aggressive NHL patient population results in a great deal of uncertainty with respect to patient utility. In deterministic sensitivity analysis, the manufacturer assessed the impact of a variety of health state utility values on the updated base case cost-effectiveness results. The ICERs obtained (with PAS)

ranged from £18,827 to £24,215 per QALY and are summarised in Table 3. Also presented in Table 3 are the results of an additional sensitivity analysis carried out by the ERG using utility values from final line chronic lymphocytic leukaemia patients (incorporated in ERG sensitivity analysis of the manufacturer's original submission). The ICER (with PAS) obtained from ERG sensitivity analysis was £32,760 per QALY.

Table 3. Results of manufacturer and ERG deterministic sensitivity analyses of health state utilities – with PAS (adapted from manufacturer's PAS submission, Table 11, pg 23)

Description of data sources	Progression free survival utility	Progressed disease utility	ICER (£/QALY)
Base case			
2nd line treatment in patients with renal cell carcinoma	0.76	0.68	£23,796
Manufacturer's alternative utility scenarios			
2nd line treatment in patients with chronic myelogenous leukaemia,	0.85	0.73	£20,385
3rd line treatment in patients with chronic lymphocytic leukaemia	0.65	0.47	£23,064
1st line maintenance treatment in patients with Follicular lymphoma	0.78	0.62	£20,692
1st line treatment in patients with metastatic renal cell carcinoma	0.70	0.59	£24,322
Self-reported quality of life during chemotherapy in elderly patients with aggressive non-Hodgkin lymphoma	0.81	0.60	£18,827
2nd line treatment in patients with malignant melanoma	0.80	0.76	£24,215
ERG's alternative utility scenario			
Final line treatment in patients with chronic lymphocytic leukaemia	0.428	0.279	£ 32,760
Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year.			

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 £30,681 per QALY (with PAS). The scatter plot of cost-effectiveness results (with PAS) and cost-effectiveness acceptability curves (with PAS) are displayed in Figures 1 and 2, respectively. According to the manufacturer's probabilistic analysis, pixantrone (with PAS) was associated with a 45.7% and 51.5% 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 PAS) falling in each quadrant of the cost-effectiveness plane is summarised in Table 4. The ERG considers it important to note that, although 70% of probabilistic iterations estimated that pixantrone was associated with greater benefit than TPC, 27.7% of probabilistic iterations indicated that patients treated with pixantrone fared worse

than those treated with TPC. Furthermore, in those simulations in which pixantrone was estimated as being associated with a QALY loss, the magnitude of that QALY loss was up to 1.26 QALYs.

Figure 1. Scatter plot of probabilistic cost-effectiveness results of pixantrone (with PAS) compared with treatment of physician's choice (adapted from manufacturer's PAS submission, Figure 5, pg 26)

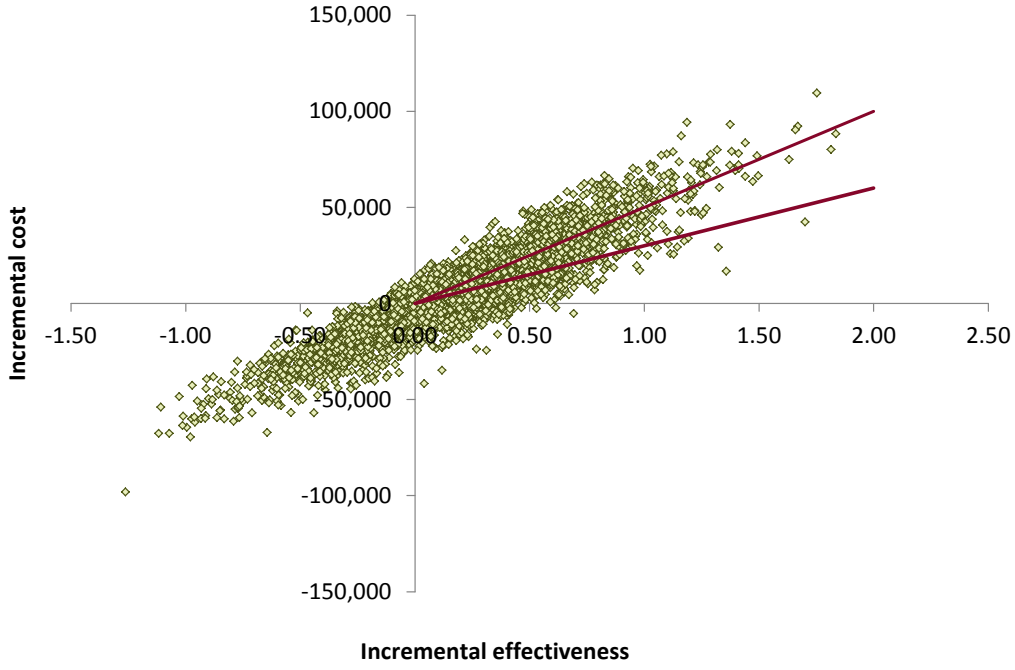

Figure 2. Cost-effectiveness acceptability curves for pixantrone (with PAS) and treatment of physician's choice (adapted from manufacturer's PAS submission, Figure 6, pg 27)

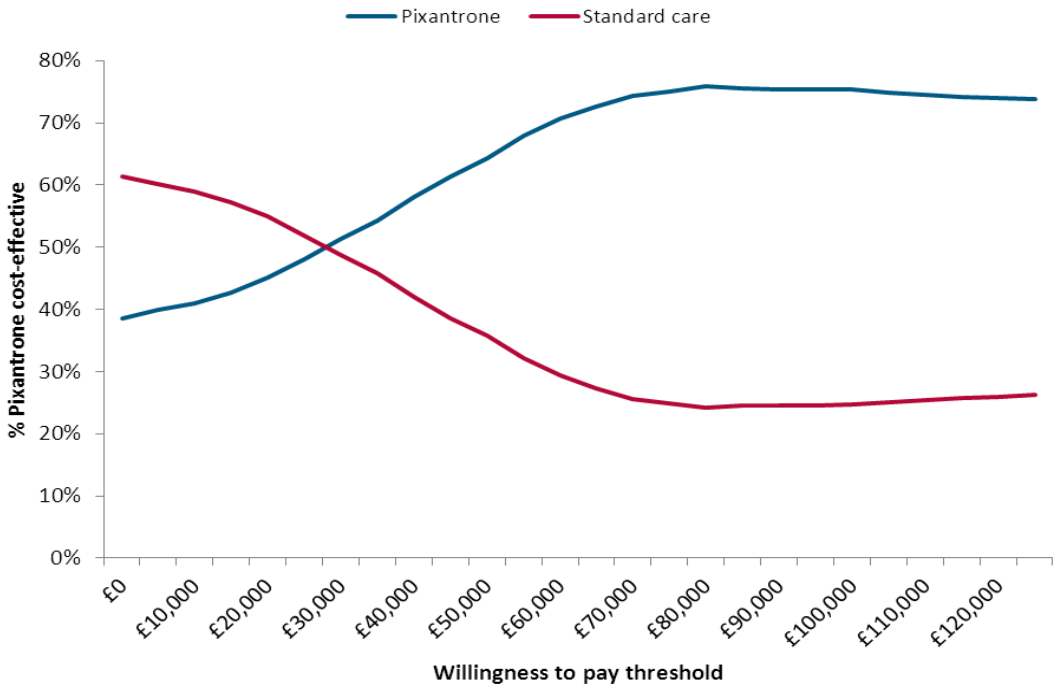

Table 4. Percentage of probabilistic simulations (pixantrone [with PAS] vs TPC) falling in each quadrant of the cost-effectiveness plane (reproduced from manufacturer's PAS submission, Table 12, pg 26)

Quadrant	Percentage of iterations
Quadrant I – Pixantrone has higher costs and higher effectiveness	58.8%
Quadrant III – Pixantrone has lower costs and lower effectiveness	27.7%
Quadrant IV – Pixantrone is dominant (i.e. has lower costs and higher effectiveness)	11.5%
Quadrant II – Pixantrone is dominated (i.e. has higher costs and lower effectiveness)	2.0%
Abbreviations used in table: PAS, patient access scheme; TPC, treatment of physician's choice.	