Response to:

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Appraisal Consultation Document

Pixantrone monotherapy for treating relapsed or refractory aggressive non-Hodgkin's lymphoma [ID414]

Prepared by:

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Summary

CTI Life Sciences (CTILS) are in receipt of the Appraisal Consultation Document (ACD) for pixantrone and remain committed to working with NICE to ensure that pixantrone can be made available to those patients in England and Wales for whom there is no licensed alternative treatment option at this time.

Following review of the document, we believe that there are four issues to address in the document this response presents additional information for the Committee to consider.

- Those regarding the patient population (Section 1)
    - Retrospective histological review of disease (Section 1a)
    - Prior use of rituximab (Section 1b)
- Those regarding the trial design of PIX301 (Section 2)
- Those regarding the clinical effectiveness of pixantrone (Section 3)
- Those specifically relating to the model (Section 4)

The comments of the Evidence Review Group (ERG) on the model have been noted and where applicable, addressed in a revision of the model submitted with this response.

Furthermore the conditional licence via the EMA process was granted based on the benefit in third and fourth line and not fifth line and beyond for which the EMA noted there was no benefit demonstrated. Given the potential for interpretation and the importance that CTILS be responsible in assuring it is promoting only within the licensed population CTILS engaged regulatory counsel to review the SPC and EPAR and CHMP correspondences. That review confirmed that the licensed patient population excludes use in fifth line or beyond. It is for this reason that the model has been developed using the subgroup of patient receiving third or fourth line therapy. CTILS would also like to respectfully point out that research into treatment practices by physicians in England demonstrates physicians do not tend to treat patients beyond fourth line offering such patients participation in clinical trials or palliative care.

Based on the assessment above and the efficacy data presented in Table 5 (Section 3 of this document, page 8) CTILS would also request that the Committee reassess their decision on end of life status for pixantrone.

CTILS look forward to continue working with the NICE process to gain a positive recommendation for pixantrone and hope that this response document and accompanying model assist the Committee in its review.

Section 1: Patient population

Section 1b: Prior use of rituximab

The prior use of rituximab in patients enrolled in the PIX301 trial is mentioned multiple times:

CTILS have noted the concerns raised by the Committee and have submitted a revised model both with and without prior use of rituximab, alongside this response. The key results from this model are shown in Table 1.

Table 1: Summary of results from the revised economic model with subgroup analysis for HITT population and with and without prior use of rituximab and ITT population

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) (LYG)	ICER (£) (QALYs)
HITT 3rd and 4th line								
Undiscounted								
pixantrone	£67,578	1.98	1.46	£20,917	0.80	0.62	£26,125	£33,551
Comparator	£46,662	1.18	0.83					
Discounted								
pixantrone	£62,073	1.77	1.31	£18,675	0.67	0.53	£27,720	£35,326
Comparator	£43,398	1.10	0.78					
HITT all lines with prior rituximab								
Undiscounted								
pixantrone	£42,766	1.08	0.80	£474	- 0.01	0.03	Dominated	£15,993
Comparator	£42,292	1.09	0.77					
Discounted								
pixantrone	£40,913	1.01	0.75	£2,244	0.01	0.04	£151,951	£52,178
Comparator	£38,669	1.00	0.71					
HITT 3rd or 4th line prior rituximab								
Undiscounted								
pixantrone	£50,084	1.26	0.93	£8,918	0.25	0.22	£35,270	£40,767
Comparator	£41,165	1.01	0.71					
Discounted								
pixantrone	£47,607	1.17	0.87	£9,170	0.23	0.20	£39,243	£45,282
Comparator	£38,437	0.94	0.66					
HITT all lines without prior rituximab								
Undiscounted								
pixantrone	£64,882	1.83	1.34	£17,053	0.59	0.47	£28,729	£36,525
Comparator	£47,828	1.24	0.87					
Discounted								
pixantrone	£59,331	1.64	1.20	£15,531	0.50	0.40	£30,882	£38,937

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) (LYG)	ICER (£) (QALYs)
Comparator	£43,800	1.13	0.80					
ITT 3rd and 4th line								
Undiscounted								
pixantrone	£97,576	2.83	2.05	£22,552	0.90	0.70	£25,035	£32,345
Comparator	£75,024	1.93	1.35					
Discounted								
pixantrone	£84,703	2.42	1.76	£18,494	0.71	0.56	£26,093	£33,272
Comparator	£66,209	1.71	1.20					

Section 3: Clinical effectiveness

ACD Section 3.38 and 3.39 Clinical efficacy

ERG had reservations about whether pixantrone had been shown to have superior efficacy in the PIX301 trial. Consequently, it felt that results from the full trial population might not reflect the benefit of pixantrone in patients with aggressive B-cell lymphoma

In recognition of the concerns regarding clinical efficacy, CTILS would like to remind the Committee of the results from the PIX301 trial for the HITT population for all lines of therapy and for the HITT population third and fourth line only, the latter of which is in line with the license. Both are presented both with and without prior rituximab.

Table 2: Summary of efficacy for HITT population all lines of therapy, without prior rituximab [10]

	Pixantrone (n=50)	Comparator (n=47)	HR (95% CI)
CR/Cru, n (%)	9 (18)	4 (8.5)	-
CR, n (%)	7 (14)*	0	-
ORR†	18 (36)*	8 (17)	-
Median PFS, months‡	5.6	2.5	0.51 (0.33,0.78)
Median OS, months‡	8.1	6.3	0.72 (0.45,1.13)

*pixantone vs comparator $p < 0.05$

HR=hazard ratio

†Responses included patients with complete, unconfirmed complete, or partial response

‡Kaplan-Meier analysis

Table 3: Summary of efficacy for HITT population third or fourth lines of therapy, without prior rituximab [10]

	Pixantrone (n=39)	Comparator (n=39)	HR (95% CI)
CR/Cru, n (%)	9 (23.1)*	2 (5.1)	-
CR, n (%)	7 (17.9)*	0	-
ORR†	17 (43.6)*	5 (12.8)	-
Median PFS, months‡	5.7	2.8	0.44 (0.27,0.71)
Median OS, months‡	11.9	7.0	0.67 (0.4,1.12)

*pixantone vs comparator p < 0.05

HR=hazard ratio

†Responses included patients with complete, unconfirmed complete, or partial response

‡Kaplan-Meier analysis

Table 4: Summary of efficacy for HITT population all lines of therapy, with prior rituximab

	Pixantrone (n=30)	Comparator (n=26)	HR (95% CI)
CR/Cru, n (%)	6 (20)	3 (11)	-
CR, n (%)	5 (17)	0	-
ORR†	9	5	-
Median PFS, months‡	3.5 (0.7-24.0)	4.6 (0.1-24.0)	0.66 (0.38,1.14)
Median OS, months‡	6.0 (0.8-24.0)	4.6 (0.1-24.0)	0.85(0.48,1.50)

*pixantone vs comparator p < 0.05

HR=hazard ratio

†Responses included patients with complete, unconfirmed complete, or partial response

‡Kaplan-Meier analysis

Table 5: Summary of efficacy for HITT population third or fourth lines of therapy, with prior rituximab

	Pixantrone (n=25)	Comparator (n=25)	HR (95% CI)
CR/Cru, n (%)	6 (24)	1 (4)	-
CR, n (%)	5 (20)*	0	-
ORR†	11	3	-
Median PFS, months‡	4.3	2.8	0.83 (0.46, 1.50)
Median OS, months‡	10.2	6.1	0.90 (0.47,1.75)

*pixantone vs comparator $p < 0.05$

HR=hazard ratio

†Responses included patients with complete, unconfirmed complete, or partial response

‡Kaplan-Meier analysis

Based on the results in Table 5, and as noted at the beginning of this document, CTILS would request that end of life status for pixantrone is reviewed.

Section 4: Issues surrounding the economic model

As mentioned previously various modifications have been implemented in the model:

- The AE disutilities recommended by ERG have been included;
- According to the recently published (4th April 2013) Guide to the methods of technology appraisal 2013[1], the drug prices have been taken from the eMIT database;
- Utilities for the two health states have been revised using those from renal cell carcinoma 2nd and subsequent line treatment.
- The following subgroups have been incorporated:
    - HITT patient populations with patients starting 3rd/4th line according to the MA,
    - HITT patient populations with patients who had prior rituximab treatment and were starting on 3rd/4th line,
    - HITT patient populations on any line of treatment for sensitivity analyses,
    - HITT patient populations with patients who had prior rituximab treatment and were starting on any line of treatment for sensitivity analysis,

In the subgroup analyses the following inputs were modifies based on the patient level data from the PIX301 trial:

- Kaplan-Meier curve estimates and the parameters and variance-covariance matrices of the distributions for progression-free survival
- Kaplan-Meier curve estimates and the parameters and variance-covariance matrices of the distributions for overall survival
- Kaplan-Meier curve estimates for treatment discontinuations
- AE rate for all HITT populations are assumed to be the same as for the HITT all lines patient population

Assumptions reported in the Manufacturer submission would apply for these subgroups also.