National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Pixantrone monotherapy for the treatment of relapsed or refractory aggressive non-Hodgkins lymphoma [ID414]

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from *BMJ* to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by **5pm, *Friday 22 February 2013*** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Major Issues

Issue 1 Pixantrone as monotherapy in the licensed indication

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pixantrone is indicated as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive Non-Hodgkin B-cell Lymphomas (aNHL). The benefit of pixantrone treatment has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy. The focus of the ERG report includes patients outside of the indication for pixantrone as it includes patients with more than 4 prior therapies (fifth line or greater). The HITT population was used per Statistical Analysis Plan as a secondary analysis and includes the subset of patients for whom consensus agreement was obtained from central independent panel that the histology was consistent with aNHL. This does not negate the determination by the site pathologist that a given patient had aNHL and is consistent with the concordance	The ERG should exclude the analysis for the entire HITT population and re-run their analyses using either the ITT B-cell population or the HITT B-cell population both restricted to 3rd and 4th line patients, which is the licensed population and a subset of the licensed population respectively.	The approved indication for pixantrone includes the statement that benefit has not been demonstrated with patients receiving it as 5th line or greater therapy. This is also in line with the NICE Reference case which states that technology should be appraised within their licensed indication: *"The population for whom the technology is being appraised is defined as precisely as possible. When the technology is a medicine, this will usually be determined by the therapeutic indications specified in the marketing authorisation. The scope may highlight potential subgroups of the population for whom the clinical or cost effectiveness of the technology might be expected to differ from the overall population or subgroups that require special consideration."* *"The Appraisal Committee does not normally make recommendations regarding the use of a drug outside the terms of its marketing authorisation, as published in the*	No change required. Not a factual inaccuracy. The ERG acknowledges that the licence for pixantrone does not specify confirmation of disease prior to treatment but, based on guidance on Improving Outcomes in Haematological Cancers (IOHC; reference supplied) together with clinical expert opinion, the ERG considers that confirmation of disease prior to initiation of treatment would be typical clinical practice in the UK. The IOHC guidance recommends that "in order to reduce errors, every diagnosis of possible haematological malignancy should be reviewed by specialists in diagnosis of haematological malignancy. Results of tests should be integrated and interpreted by experts who work with local haemato-oncology multi-disciplinary teams (MDTs) and

generally reported in the literature. The marketing authorisation does not require central histologic confirmation of the diagnosis and in addition this is not clinical practice. If the HITT population is to be used for the model, then it should be restricted to patients who received pixantrone as 3rd or 4th line of therapy as specified in the indication as per Table 15 of the STA report and not include all lines of therapy as per the ERG report.		*manufacturer's summary of product characteristics. It can, however, consider unlicensed comparator technologies if these are used regularly in the NHS. Long-standing treatments often lack a sponsor to support the licensing process. In exceptional cases, the Appraisal Committee may make recommendations outside of the marketing authorisation if directed to do so by the Department of Health."(NICE 2008).*	provide a specialised service at network level. This is most easily achieved by locating all specialist haemato-pathology diagnostic services in a single laboratory". In addition, given that the ITT B-cell population includes 126 patients compared with 97 patients in the retrospectively confirmed aggressive B-cell population, the ERG considers that the ITT B-cell population potentially includes patients without aggressive B-cell NHL. Considering the number of prior chemotherapeutic regimens, the ERG notes that the conditional approval issued by the CHMP states "Pixuvri is indicated as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive Non-Hodgkin B-cell Lymphomas. The benefit of pixantrone treatment has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy". The ERG considers that this statement does not preclude use of pixantrone as a fifth or subsequent line treatment in

			multiply relapsed or refractory NHL.

Issue 2 The utility data selected by the ERG being inappropriate, and lacking face validity

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 97-98 "Based on expert clinical advice, the ERG considers the population of patients on third-line treatment for chronic lymphocytic leukaemia (reported in Ferguson *et al*. (53)) to be most representative of the population of patients considered in the manufacturer's model." CTI assert that the population referred to, that of chronic lymphoid leukaemia, is not appropriate (see Justification for detail). "ERG considers that the utility values reported for patients on "final line therapy" may be more representative of the patient population that is the focus of this STA." CTI considers the publication referred to (Fergusson et al. 2008) to be an unsuitable source of utility values (see Justification for detail).	CTI recommends the revision of these sentences, so that the utility data from Ferguson et al. 2008 is used only in sensitivity analysis as an extreme value.	<u>Methodological issues</u>: The utility values recommended are not appropriate according to the NICE reference case, since they are elicited from general population using time-trade off (TTO), as opposed to the requirement of patient reported values using EQ-5D. *"For the reference case, the measurement of changes in HRQL should be reported directly from patients and the value of changes in patients' HRQL (that is, utilities) should be based on public preferences using a choice-based method. The EQ-5D is the preferred measure of HRQL in adults."(NICE 2008)* The detailed methodology of the utility elicitation and the exact vignettes that has been used for the description of health states cannot be assessed for appropriateness, as data was published only in the form of a conference abstract. <u>Face validity issues:</u> The values	No change required. Not a factual inaccuracy. All analyses presented by the ERG are sensitivity analyses of the manufacturer's base case. In addition, the ERG selected the utility values reported for final line therapy based on expert clinical advice that, of the patient populations identified in the manufacturer's literature review, a 3rd line CLL patient population would be most representative of the patient population that is the focus of this STA.

		reported here and elicited by TTO are significantly lower than the utility values elicited in oncology using the methodology requested in the NICE reference case. A structured literature review of EQ-5D utilities in oncology reported values ranging from 0.33 (SD 0.4) to 0.93 (SD 0.12), with the lower value for cancer related anorexia/cachexia syndrome and oxidative stress (Pickard et al, 2007). The value used by ERG for post-progression (0.278) is lower than the value for paralysis 0.350 (95% CI: 0.236-0.465) estimated for the Catalogue of EQ-5D Scores for the United Kingdom by Sullivan et al. (2011). CTI recognised, that although the indication for the utility values selected for base case in the Manufacture's submission is the most appropriate, it is elicited from earlier line of treatment, thus potentially an overestimation. As a result CTI provided a range of values for sensitivity analysis ranging from 0.47-0.85. <u>CLL is not a representative disease</u>: CLL in post-second and "final line therapy" is not comparable to aNHL (Ferguson 2008) due to the chronic nature of the disease and associated complications (anaemia,	

		thrombocytopenia, recurrent infections including CMV, Herpes Zoster with chronic post herpetic neuralgia requiring chronic pain management), all of which have a higher healthcare utilisation requirement and quality of life impact than multiply relapsed Non-Hodgkins Lymphoma. In particular, the frequent and persistent infections and fatigue/anaemia in late stage CLL have a large impact on pain, usual activities, mobility, and the cumulative cost of care.	

Issue 3 All patients will have received prior rituximab

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG state on page 14 and throughout the report, that all UK patients will have received rituximab "as a component of their standard care". This statement is true in 2013. The PIX 301 study was started in 2004 prior to inclusion of rituximab as part of standard of care in aggressive B cell lymphoma treatment. As rituximab became available in various territories as standard of care for this disease, the protocol was amended to ensure that all patients received rituximab prior to randomisation if	The ERG in their analyses, should use the data set from the licensed patient population (3rd or 4th line) either the HITT B-cell sub set population patients, or the ITT licensed population of aggressive B-cell NHL 3rd or 4th line setting (Table 16 of the BMJ Technology Assessment Group Report).	Table 16 of ERG report cited that median OS and PFS were in favour of pixantrone compared to TPC whether they have been treated with or without prior rituximab in 3rd and 4th line treatment in the HITT subset population. This is the patient population for which the marketing authorisation was approved. Analysing the HITT-B cell subset across all lines of therapy includes patients outside the labelled population and is not consistent with the NICE reference case (see Issue 1).	No change required. Not a factual inaccuracy. The ERG considers that its remit is to present data pertaining to current UK clinical practice. As highlighted by the manufacturer, current guidance is to incorporate rituximab as part of a first-line treatment regimen for aggressive NHL and, thus, the subgroup of patients who have received prior treatment with rituximab is particularly relevant to the decision problem that is the

it was available. In all, 52% of patients enrolled in PIX 301 received rituximab before study entry The patient population specified in the SmPC are aggressive B-cell NHL patients receiving pixantrone as third or fourth line therapy. The benefit of pixantrone in 5th line therapy has not been established Therefore in evaluating the efficacy of pixantrone in patients with prior rituximab, ERG should only include the labelled population (3rd and 4th line setting and not 5th line and beyond).			focus of this STA. As noted above, based on guidance on IOHC and expert opinion, histological confirmation of disease before treatment is recommended UK clinical practice. In addition, the ERG considers that the conditional approval issued by the CHMP does not preclude use of pixantrone as a fifth and subsequent line treatment.

Issue 4 The economic model is biased towards pixantrone

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15, page 80 table, page 119 The report states, that the PFS benefit has been overestimated or that the analysis appears to be biased.	"For PFS, the model overestimates the difference between the medians due to the steps seen in the Kaplan-Meier curves around the median."	As described in section 7.7.1 of the Manufactures submission: "For PFS, the model overestimates the median for the pixantrone arm and slightly underestimates it for the comparator arm. This is due to the steps seen in the Kaplan-Meier curves at the median (please see section 7.37). These steps have been smoothed out for the model." The overestimation of the difference in PFS is at one point along the	Based on the comparison of median values, which as the manufacturer states are overestimated for pixantrone and underestimated for TPC, the ERG considers that the model **may** be biased towards pixantrone. No definite statements about bias have been made by the ERG on page 80 or page 119. However, the ERG notes that the word "potentially" has been

		curve, and does not imply the overestimation of the difference between the area under the curve, which is used in calculations. In addition the selected distribution fitted the IPD data well both statistically and graphically with its face validity was confirmed by expert opinion.	omitted from the summary on page 15 and has amended the statement accordingly.

Minor Issues

Issue 5 Over interpretation of subgroup data including patients outside of the licensed population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On multiple pages, and on multiple issues, we believe the ERG has focussed on and draws conclusions from comparisons that are unreliable due to the small numbers of patients and include patients who are excluded from the labelled population, examples are - The number of patients having received prior rituximab in Western Europe (P15) - The characteristics and survival of Western European patients alone (P45) - The different disease subtypes included in the model (P81)	Interpretation of subset analyses consisting of small numbers of patients are not reliable as evidenced by the wide confidence intervals. Analyses in this setting should be limited to descriptive and such changes should be made throughout the document. A lesser focus on the over-interpretation on small patient numbers should be made throughout the report. The size of the sample should be reported throughout for comparisons. In addition subset analyses should only include the labelled patient population and results should be limited to this subset of 3rd and 4th line. For example Page 137 states: "In the subgroup of patients who had received prior rituximab treatment and had histological confirmation of aggressive B-cell NHL, there was no statistically significant difference between pixantrone and TPC in any clinical outcome" This statement is not accurate as the analyses conducted included patients outside of the labelled population (i.e. 5th line and beyond).	By reporting the sample sizes, the reader can easily judge the credibility of the statement, and level of evidence supporting it. Commenting on statistical significance in post hoc subset analyses among small numbers of patients are both unreliable and non-interpretable. Observed trends between the patient subsets would be more appropriate.	No change required. Not a factual inaccuracy. In the Executive summary (pg 15), the ERG states: "Comparative clinical effectiveness results for most subgroups presented (e.g., histologically confirmed aggressive B-cell NHL, prior treatment with rituximab, and geographic region) are based on *post ho*c subgroup analyses. Moreover, as subgroups, the power to detect a difference is reduced further, the number of patients in the analysis is generally small, and there is increased uncertainty around the robustness of the result. In the case of subgroups based on retrospective histological confirmation of disease and prior rituximab treatment, because randomisation was not stratified by these factors, there is the potential for unbalanced groups. For these

			reasons, the ERG considers that results of the subgroup analyses should be interpreted with caution." The ERG considers that this statement appropriately addresses the concerns raised by the manufacturer around the interpretation of *post hoc* subgroup analyses.

Issue 6 Errors in describing the economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13 The presentation of 95% confidence intervals (CIs) for ICERs	CTI recommends the deletion of text referring to CIs for ICERs or the addition of an explanation of the method used to estimate it and the caveat, that the cost-effectiveness acceptability curve (CEAC) is considered better guidance for decision-makers	There is no straightforward way to estimate CIs for ICERs, due to the correlation between the costs and benefits. Various methods have been proposed and challenged. However the consensus remains, that due to the limitations of CIs, or credible intervals (Briggs et al. 2006) for ICERs, the CEAC is a more appropriate way of representing uncertainty around the ICER than CIs.(Maiwen 2012, Wang 2008, Briggs et al. 2006)	The ERG considers it important to present the 95% CIs along with the mean result to highlight the high level of uncertainty in the mean result. However, the ERG acknowledges the variability in methods used to assess 95% CIs and has therefore added an explanation of the calculation method used to page 8 of the report.
Page 78, table 22 For the synthesis of evidence on outcomes, the table states that IPD data was used for treatment discontinuation and efficacy	"Yes. Systematic literature review was carried out for efficacy, safety, cost and HRQL outcomes. Due to lack of data, IPD data were used to inform treatment discontinuation and efficacy outcomes, expert opinion and publicly	Systematic literature reviews were carried out as recommended in the reference case. No data were found for discontinuations, efficacy, safety and costs in the literature.	No change required. Not a factual inaccuracy. IPD data were used to inform efficacy and discontinuation.

outcomes and systematic literature review was carried out for costs and HRQL	available databases to inform costs."		
Page 95 The report mentions Manufacturer's Appendix Z; Table 2.4.7 and 2.4.8"	Correction of the typo	The Manufacturer's submission contains Appendices A-Q.	No change required. Not a factual inaccuracy. Appendix Z was provided by the manufacturer at clarification.
Page 105 "The ERG notes that the calculation of drug costs to include wastage was partially hard coded within the manufacturer's model and therefore unable to be fully validated."	The sentence should be deleted	The wastage calculations are estimated with the help of the SolverWastage VB macro written in the model, thus are not hard coded. The macro is accessible in the Visual Basic interface. Only the patient level data on the BSA patient level sheet, which are used for the calculations, are hardcoded.	No change required. Not a factual inaccuracy. The ERG notes that some values (for example "Max doses to allow choice") used in the wastage calculations (including patient level data) were hardcoded into the "Wastage" sheet in the Excel file. Consequently full validation of the calculations could not be carried out.
Page 109, table 37 The duration for hospice care is given as annual	CTI recommends changing it to 28 days	The duration for the hospice use is per 28 days. The duration for the unit cost is per day.	The ERG thanks the manufacturer for highlighting this inaccuracy and has amended Table 37 accordingly.

Page 109 onwards In the resource use tables, no time period is given	Insertion of the time period the resources are applicable for, e.g. 28 days.	As the model cycle is 1 week, without the time period given (though implied in the footnote), the resource use gives the impression to be also applicable for 1 cycle.	No change required. Not a factual inaccuracy. The time period for each resource use is given in the table headings.
Page 131, table 58 "Treatment effectiveness in a patient population previously treated with rituximab" - "Not assessed, likely to result in a substantial ICER increase due to reduced benefit in this patient population"	CTI recommends the revision of the second sentence as follows: "Not assessed, due to the small patient population"	Please refer to Issue 5 for further detail.	No change required. Not a factual inaccuracy. Based on examination of the clinical subgroup analyses carried out in this patient population, the ERG observed a trend towards decreased effect of pixantrone versus TPC, which would result in an increase in the ICER.
Page 131, table 58 "The use of OS data from combination rather than monotherapies" - "No data available to inform this, however likely to result in a small increase in the ICER as a result of a prolonged sojourn in the "PD" health state"	CTI recommends the revision of the second sentence as follows: "No data available to inform this, direction of change in ICER is uncertain, but likely to be small"	Although post-progression survival might be longer with combination therapies, this health state also has substantial costs, and the combination therapies would have higher drug and administration costs. The direction of change in ICER depends on how the additional survival relates to the additional costs. Without additional analysis, the direction is uncertain.	No change required. Not a factual inaccuracy. The ERG notes that both the increased cost and the possible increased survival resulting from the use of combination rather than monotherapies would be applied to both arms. Furthermore, based on sensitivity analyses carried out by the manufacturer, which revealed that the relative QALY benefit of pixantrone over TPC is accrued in the PFS health state, the ERG

			maintains the opinion that an increased time in the “PD” health state is likely to increase the ICER of pixantrone versus TPC.

Issue 7 Lack of clarity regarding cardiology outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 12 the ERG report states: “An independent cardiology review identified that there were 14 events (in 13 patients) considered likely (9 events in nine patients) or possibly (5 events in four patients) to be associated with pixantrone treatment, including two putative cases of congestive heart failure.” It should be noted that this review was retrospective and assignment of causality to pixantrone was not determined by the treating clinician.	The wording used is difficult to understand, we suggest it be reformatted to read: “An independent retrospective review of cardiotoxicity by an independent expert identified that there were 14 events (in 13 patients) which met the predefined conditions for an event**.** These included all declines of left ventricular ejection fractions of >10% whether or not they were considered adverse events by the treating physician. Nine events in nine patients, were considered by the reviewer, likely to be associated with pixantrone treatment, and 5 events in four patients were considered to be possibly associated with pixantrone treatment, including two putative cases of congestive heart failure.” Investigator determined overall Cardiac Disorder adverse events deemed related to pixantrone occurred in 5 events among 5 patients	The lack of clarity has the potential to change the meaning of the sentence, overestimating the level of adverse events seen with pixantrone.	No change required. Not a factual inaccuracy.

References

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Ferguson J, Tolley K, Gilmour L; Priaulx J. 2008. Health state preference study mapping the change over the course of the disease process in chronic lymphocytic leukaemia (CLL): Value in Health 2008; 11(6):A485

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Pickard Simon A, Wilke Caitlyn T, Un Hsiang-Wen and Lloyd Andrew· Health Utilities Using the EQ-5D in Studies of Cancer: PharmacoEconomics 2007; 25 (5): 365-384

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Reference added by ERG

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