NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

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

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
CTI Life Sciences	The second ACD report the uncertainty around the cost-effectiveness estimates as a major issue, such as: "It noted that the manufacturer's deterministic ICER incorporating the patient access scheme for this population was £23,800 per quality-adjusted life year (QALY) gained and that the ERG's probabilistic ICER incorporating the patient access scheme for this population, which was generated using the manufacturer's model, was £30,700 per QALY gained. The Committee considered the difference between the 2 ICERs to reflect uncertainty in the cost-effectiveness estimates." "The Committee was aware that NICE's Guide to the methods of technology appraisal (2008) states that when the most plausible ICER is greater than £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources should take into account the degree of certainty around the ICER" "The Committee noted that the ERG's exploratory probabilistic sensitivity analysis showed that the probability of pixantrone being cost effective compared with treatment of physician's choice at a maximum acceptable ICER of £30,000 per QALY was only approximately 50% and that the probability was even lower at a maximum acceptable ICER of £20,000 per QALY. It agreed that this reflected a very high level of uncertainty around the ICER. The Committee understood that this was a result of the substantial uncertainty in the clinical benefit of pixantrone arising from the small patient numbers in the post-hoc subgroup. The Committee concluded that because the probabilistic ICER of £30,700 per QALY gained was above £20,000 per QALY gained (and also above £30,000 per QALY gained) and associated with substantial uncertainty, pixantrone was not recommended as a cost-effective use of NHS resources." The second PAS submission, while acknowledging the important uncertainty around the clinical inputs by offering an additional discount, also aims to highlight the issues, limitations and the difficulties of the estimation and interpretation of uncertainty around the cost-effectiveness results. The most plausible ICER is the deterministic ICER Using the most plausible model structure and assumptions the most plausible ICER is based on the set of inputs, that are the most accurate representations of 'reality', that is the most plausible inputs given our current knowledge. The values of the inputs that have been selected as most plausible are the ones used in the deterministic analysis and accepted by the committee. Thus assuming a valid model structure and set of assumptions, the most plausible ICER is the deterministic ICER. The deterministic ICER in the new PAS submission is £18,462 per QALY gained. While the deterministic sensitivity analyses shows the areas of uncertainty, the probabilistic analysis can indicate the magnitude of uncertainty. This uncertainty includes the uncertainty around the input	Comments noted. The Committee considered the different deterministic and probabilistic ICERs provided by the manufacturer that incorporated the patient access scheme submitted in November 2013. It concluded that the mean probabilistic ICER could overestimate the uncertainty associated with the survival modelling and that the true value of the most plausible ICER might be lower. See FAD sections 4.14 and 4.15.

	parameters and some of the structural uncertainty stemming from model structure and assumptions used in the calculations. This is represented in the cost-effectiveness acceptability curve (CEAC) and the scatterplot. Thus, while there is important uncertainty around the clinical parameters due to the analysis of a subgroup from the pivotal trial with small patient numbers, the uncertainty represented in the CEAC and scatterplot is the result of both parameter and structural uncertainty. For example one of the limitations of the incorporation of the lognormal survival curves in the probabilistic analysis is the assumption of independence of OS and PFS, which has been shown to be not the case in aggressive non-Hodgkin's lymphoma. This assumption leads to the two curves crossing in 30% of the simulation in the probabilistic analysis, i.e. for a time period more patients are progression-free than alive. The model in these cases artificially reduces the PFS, to avoid these scenarios. Thereby the probabilistic results incorporate not only the uncertainty in the clinical results for OS and PFS and the uncertainty from the parametric modelling of these curves, but also this technical assumption. (Please see section 3.23 of the PAS submission for further details.) In an ideal scenario, all simulations are in the north-east quadrant, where the drug is more effective and more costly (i.e. both incremental costs and incremental health benefits are positive) and the uncertainty of the probabilistic results mainly represent the parameter uncertainty. In this case with sufficient number of simulations the deterministic and the probabilistic ICER converge. However in the current submission the simulations fall in all four quadrants and the probabilistic results reflect both parameter and structural uncertainty. Thus the probabilistic results are skewed, and depending on the assumption used are either below or above the deterministic ICER. Assuming complete independence of OS and PFS leads to a probabilistic mean ICER of £22,024/QALY, and a median ICER of £14,692/QALY, while assuming OS and PFS vary between simulations together for each comparator leads to a mean ICER of £9,938/QALY. Thus the difference between the probabilistic and the deterministic ICER represents the effect of the structural uncertainty and the effect of the different interpretation of the ICERs in the different quadrants. As a result the uncertainty of the cost-effectiveness due to the uncertainty of the parameters and the assumptions are represented in the CEAC and the scatterplot. The probabilistic mean results are not an accurate representation of the most plausible scenario.	
CTI Life Sciences	**With the use of conservative assumptions overestimates the uncertainty around the results** In the probabilistic analysis and the representation of the probabilistic results various assumptions are required. Among these are the ones regarding: • Independence of OS and PFS	Comments noted. The Committee considered the different deterministic and probabilistic ICERs provided by the manufacturer that incorporated the patient access scheme submitted in November 2013. It concluded that the mean probabilistic ICER could overestimate the uncertainty associated

	• Independence of the efficacy between the comparator arms • Distribution of incremental QALYs and incremental costs • Independence of costs and QALYs In these cases conservative assumptions were used, that would result in the overestimation of the uncertainty represented in the probabilistic analysis. (Please see section 3.23 of the PAS submission for further details.) Similarly in the deterministic sensitivity analyses extreme values were tested to assess the effect of the different inputs and assumptions on the cost-effectiveness results. This, if used to assess the magnitude of uncertainty, would lead to overestimation. (Please see section 3.22 of the PAS submission for further details.)	with the survival modelling and that the true value of the most plausible ICER might be lower. See FAD sections 4.14 and 4.15.
Lymphoma Association	The Lymphoma Association notes the conclusions drawn by the Appraisal Committee, after its second meeting, not to recommend pixantrone within its marketing authorisation despite the additional evidence provided by the manufacturer and the proposed patient access scheme. As we have commented previously, this decision will be a disappointment to people with aggressive NHL who don't respond well to, or relapse after, two standard courses of treatment. People in this situation, as the committee acknowledged, face an incredibly difficult future as there is no standard of care. There is a huge unmet need for this patient population. Clinicians and their patients are currently making difficult treatment decisions based on limited clinical evidence. Pixantrone is the only licensed treatment option for this indication and the alternative treatment options currently used in England and Wales have no stronger or more conclusive evidence to support their use for this group of patients. We urge the manufacturer and NICE to continue exploring whether it is possible to achieve a patient access scheme that will enable NICE to approve the use of pixantrone in order to improve the treatment options for this poorly served group of patients.	Comments noted. . Following the submission of a patient access scheme (November 2013), the Committee concluded that the most plausible ICER was likely to be less than £22,000 per QALY gained and therefore pixantrone was recommended as a cost-effective use of NHS resources. See FAD section 4.15.
Royal College of Nursing	There are no comments to submit on behalf of the Royal College of Nursing to inform on the ACD consultation of the above appraisal.	Comment noted. No changes to the FAD requested or required.
Department of Health	I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Comment noted. No changes to the FAD requested or required.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Consultation on the second appraisal consultation document		
Royal College of Physicians	I agree with the conclusions of this report. My only comment is that the manufacturer should probably be challenged as to the quoted timelines for the PIX 306 study as the statement that results will be available in 2015 seems rather optimistic to me.	Comments noted. Following the submission of a patient access scheme (November 2013), the Committee concluded that the most plausible ICER was likely to be less than £22,000 per QALY gained and therefore pixantrone was recommended as a cost-effective use of NHS resources. See FAD section 4.15. June 2015 is the current expected date of publication of the study.

Comments received from commentators

No comments were received from commentators.

Comments received from members of the public

No comments were received from members of the public.