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

Response to second Appraisal consultation document and revised patient access scheme submission: Uncertainty in the pixantrone cost-effectiveness model

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 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.

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
- 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.)