# Review of TA306; Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma

TA306 was published in February 2014 and scheduled to be considered for review following the publication of PIX306 trial results.

## 1. Decision

The guidance remains relevant and an update is not needed.

## 2. Rationale

No substantial new evidence has been identified that would be likely to change the current recommendation in TA306.

## 3. Summary of new evidence and implications for review

### *Has there been any change to the price of the technology(ies) since the guidance was published?*

The company has confirmed that the discount for pixantrone is still in place and this is not anticipated to change.

### *Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?*

There are no anticipated changes to the marketing authorisation that would affect the existing guidance. In April 2019, the Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion for the renewal of pixantrone to convert its conditional approval into a standard marketing authorisation.

### *Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?*

In TA306, the committee concluded that there was considerable uncertainty around the clinical results. The key clinical trial informing the appraisal was PIX301 which compared pixantrone with ‘physician’s choice of single-agent chemotherapy’ for

aggressive non-Hodgkin's lymphoma that had relapsed after 2 or more chemotherapy regiments. The committee concluded that PIX301 was underpowered but suggested an increase in response rates, progression-free survival (PFS) and overall survival (OS) for pixantrone compared with treatment of physician's choice in the subgroup appropriate for decision making, but that these results were not statistically significant. The committee also concluded that there was limited and non-robust evidence to show that pixantrone was more clinically effective than treatments currently used in the committee's preferred subgroup. However, the committee agreed that the most plausible ICER in the subgroup most appropriate for decision making was likely to be less than £22,000 per quality-adjusted life-year gained.

As part of this review, 1 new relevant randomised controlled trial (RCT) was identified, which described the results of the PIX306 clinical trial (Pettengell et al. 2019)[1]. The committee in TA306 noted that PIX306 was an ongoing clinical trial and that the population was relevant to the appraisal. It recommended that TA306 should be considered for review upon publication of the results of PIX306. PIX306 is a phase 3, single-blind RCT conducted in adults with aggressive B-cell non-Hodgkin's lymphoma who had relapsed after 1 or more rituximab-containing regimens and were not eligible for a stem cell transplant. People with primary refractory disease were excluded. Two-thirds (66.6%) of participants had received either 0 or 1 previous lines of chemotherapy and one-third (33.3%) of participants had received 2 or 3 previous lines of chemotherapy. Participants were randomised to receive either pixantrone plus rituximab or gemcitabine plus rituximab. Median PFS was 7.3 months (95% confidence interval [CI] 5.2 to 8.4 months) with pixantrone plus rituximab compared with 6.3 months (95% CI 4.4 to 8.4 months) with gemcitabine plus rituximab (hazard ratio [HR] 0.85, 95% CI 0.64 to 1.14). Median OS was 13.3 months (95% CI 10.1 to 19.8 months) with pixantrone plus rituximab compared with 19.6 months (95% CI 12.4 to 31.9 months) with gemcitabine plus rituximab (HR 1.13, 95% CI 0.83 to 1.53). The authors note that the study was underpowered for the PFS analysis and that OS data are based on an interim analysis of 177 events and are not mature enough to capture the long-term effect of treatment.

The results of PIX306 do not address the uncertainty the committee noted in the clinical efficacy results during TA306, as the trial did not show any statistically significant differences in PFS or OS. The majority of participants in PIX306 received either 0 or 1 previous lines or chemotherapy. However, the marketing authorisation for pixantrone is for the treatment of multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphoma. Therefore, PIX306 is potentially not representative of the population included in TA306.

In summary, the new evidence is unlikely to lead to a change in the recommendation of the original guidance, given the remaining uncertainties in the evidence and the applicability of this new evidence to the population in this appraisal.

### *Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?*

Since publication of TA306, 3 NICE technology appraisals have been published and there are 2 ongoing NICE technology appraisals (for lisocabtagene maraleucel and tafasitamab with lenalidomide), at the same point of the treatment pathway as pixantrone. Axicabtagene ciloleucel (TA559) and tisagenleceucel (TA567) are recommended within the Cancer Drugs Fund for relapsed or refractory large B-cell lymphoma in adults after 2 or more systemic therapies and polatuzumab vedotin with rituximab and bendamustine (TA649) is recommended for relapsed or refractory large B-cell lymphoma in adults who cannot have haematopoietic stem cell transplant. The committee in TA306 concluded that there is wide variation in choice of third- and fourth-line treatment options for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma and that ‘physician choice’ was an appropriate comparator. The publication of TA649 may have implications for the appropriate choice of comparator in TA306, as this technology is recommended for routine commissioning. However, the inclusion of polatuzumab vedotin as a comparator to pixantrone is unlikely to lead to changes in the current recommendation.

### *Additional comments*

The committee in TA559 concluded that pixantrone is rarely used in clinical practice and should not be considered a comparator to axicabtagene ciloleucel for treating

adults with aggressive non-Hodgkin's B-cell lymphoma that has relapsed or been refractory to at least 2 lines of treatment.

The search strategy from the original ERG report was adapted for the Cochrane Library, Medline, Medline In-Process and Embase. References from January 2013 to November 2020 were reviewed. Additional searches of other sources were also carried out. The results of the literature search are discussed in the ‘Summary of evidence and implications for review’ section above.

## 4. Equality issues

No equality issues were identified during the appraisal.

## Proposal paper sign off

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# Appendix A – Information from existing guidance

## 1. Original remit

To appraise the clinical and cost effectiveness of pixantrone monotherapy within its licensed indication for the treatment of relapsed or refractory aggressive non-Hodgkin's lymphoma in people for whom treatment with single agent chemotherapy is being considered.

## 2. Current guidance

1.1 Pixantrone monotherapy is recommended as an option for treating adults with multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma only if:

- the person has previously been treated with rituximab and
- the person is receiving third- or fourth-line treatment and
- the manufacturer provides pixantrone with the discount agreed in the patient access scheme.

1.2 People currently receiving treatment initiated within the NHS with pixantrone monotherapy that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

## 3. Research recommendations from original guidance

N/A

# Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

| Options | Consequence | Selected – 'Yes/No' |
|---|---|---|
| A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the MTA process. | A review of the appraisal will be planned into the NICE's work programme. | No |
| The decision to review the guidance should be deferred. | NICE will reconsider whether a review is necessary at the specified date. | No |
| The guidance should be incorporated into an on-going clinical guideline. | The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance will remain in place until such time as the clinical guideline is considered for review.<br>This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal. | No |
| The guidance should be updated in an on-going clinical guideline[1]. | Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn.<br>Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation). | No |

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

| Options | Consequence | Selected – 'Yes/No' |
|---|---|---|
| The guidance remains relevant and an update is not needed. | The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. | Yes |
| The guidance should be withdrawn | The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS.<br>The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved. | No |

# Appendix C – Other relevant information

## Relevant Institute work

### *Published*

- Non-Hodgkin's lymphoma: diagnosis and management (2016) NICE guideline NG52
- Non-Hodgkin's lymphoma NICE pathway (last updated September 2020)
- Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma (2020) NICE technology appraisal guidance 649
- Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies (2019) NICE technology appraisal guidance 567
- Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies (2019) NICE technology appraisal guidance 559

### *In progress*

- Lisocabtagene maraleucel for treating relapsed or refractory aggressive B-cell non-Hodgkin lymphoma. NICE technology appraisal guidance. Publication expected June 2021.
- Tafasitamab with lenalidomide for treating relapsed or refractory diffuse large B-cell lymphoma. NICE technology appraisal guidance. Publication date to be confirmed.

## Details of changes to the marketing authorisation for the technology

### *Marketing authorisation and price considered in original appraisal*

“Pixantrone has a conditional marketing authorisation 'as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphomas (NHL). 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 European public assessment report noted pixantrone had a reduced benefit in patients pretreated with rituximab. The marketing authorisation is linked to results being provided from the phase III PIX306 trial, which is investigating pixantrone plus rituximab compared with gemcitabine plus rituximab in patients with relapsed or refractory aggressive non-Hodgkin's B-cell lymphomas who have previously received a rituximab-containing regimen. Results are expected in 2015".

"Pixantrone is priced at £553.50 per 20-ml vial containing 29 mg free base pixantrone, which is equivalent to 50 mg pixantrone dimaleate (excluding VAT; 'British national formulary' [BNF] edition 66). The estimated cost of a course of treatment is £19,926 (costs calculated over 4 cycles using an average of 3 vials per dose based on the median length of treatment in the PIX301 trial." A confidential patient access scheme is in place for pixantrone.

### *Proposed marketing authorisation (for this appraisal) and current price*

The marketing authorisation is no longer conditional (as of 6 June 2019), as the European Medicines Agency considers the specific obligations of the conditional license to have been fulfilled.

The price remains the same according to eBNF (accessed 19 November 2020).

## Registered and unpublished trials

No relevant registered or unpublished trials were identified.

## References

1. Pettengell, Ruth, et al. "Pixantrone plus rituximab versus gemcitabine plus rituximab in patients with relapsed aggressive B-cell non-Hodgkin lymphoma not eligible for stem cell transplantation: a phase 3, randomized, multicentre trial (PIX306)." *British journal of haematology* 188.2 (2020): 240-248.