NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Loncastuximab tesirine for treating relapsed or refractory diffuse large B-cell lymphoma and high-grade B-cell lymphoma after 2 or more systemic treatments

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using loncastuximab tesirine in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: September 2023

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using loncastuximab tesirine in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 24 October 2023
- Second evaluation committee meeting: 14 November 2023
- Details of the evaluation committee are given in section 4.

1 Recommendations

1.1 Loncastuximab tesirine is not recommended, within its marketing authorisation, for treating relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) after 2 or more systemic treatments in adults.

1.2 This recommendation is not intended to affect treatment with loncastuximab tesirine that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Standard treatment for relapsed or refractory DLBCL after 2 or more systemic treatments includes polatuzumab vedotin with rituximab and bendamustine (polatuzumab plus BR), and chemotherapy. There is no standard treatment for HGBL, but people are usually offered the same treatments as DLBCL.

Evidence from one clinical trial shows that some people with DLBCL and HGBL having loncastuximab tesirine have all signs and symptoms of their cancer disappear (complete remission). But it was not compared with any other treatments in the trial, so it's not known how it directly compares with standard treatment. The results from indirect comparisons of loncastuximab tesirine with other treatments are very uncertain, but suggest it is as effective as polatuzumab plus BR and more effective than chemotherapy.

Because of their similar clinical effectiveness, only the difference in cost between loncastuximab tesirine and polatuzumab plus BR was considered, and loncastuximab tesirine is much more expensive. For loncastuximab tesirine compared with chemotherapy, even when considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimates are

above what NICE normally considers an acceptable use of NHS resources. So, loncastuximab tesirine is not recommended.

2 Information about loncastuximab tesirine

Marketing authorisation indication

2.1 Loncastuximab tesirine (Zynlonta, Swedish Orphan Biovitrum) is indicated for 'the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy.'

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for loncastuximab tesirine.

Price

2.4 The list price for loncastuximab tesirine is £15,200 per 10 mg vial (excluding VAT; company submission). An average course of loncastuximab tesirine per person is £85,562.

2.5 The company has a commercial arrangement, which would have applied if loncastuximab tesirine had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Swedish Orphan Biovitrum, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

Clinical need and treatment pathway

A need for new treatment options

3.1 Both relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) are aggressive types of non-Hodgkin

lymphoma. Symptoms and treatment of the disease can have a severe impact, both physically and mentally, for people who have the disease and their carers. The clinical pathway for DLBCL after 2 or more systemic treatments is evolving. There is no standard treatment pathway for HGBL, so it often follows the same treatment pathway as DLBCL. Patient and clinical experts advised that DLBCL and HGBL can be difficult to treat and often need intensive treatment options, so it is important to have other treatment options available. The committee concluded that there is an unmet need in this population and loncastuximab tesirine offers a new potential treatment option.

Evolving treatment pathway

3.2 At the time of this evaluation, there were several recent changes to the treatment pathway for relapsed or refractory DLBCL after 2 or more systemic treatments. Polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin and prednisolone (polatuzumab R-CHP) was recently recommended for untreated DLBCL (NICE technology appraisal 874). Because polatuzumab R-CHP is now being used earlier in the treatment pathway, this will likely lead to a reduction in the use of polatuzumab vedotin with rituximab and bendamustine (polatuzumab plus BR; NICE technology appraisal 649) in the later stages of treatment. Also, chimeric antigen receptor (CAR) T-cell therapies have been recommended. Axicabtagene ciloleucel is used after 2 or more treatments (NICE technology appraisal 872) and is available in the Cancer Drugs Fund (CDF) after first-line chemoimmunotherapy (NICE technology appraisal 895), and tisagenlecleucel is available in the CDF after 2 or more treatments (NICE technology appraisal 567). Treatments in the CDF were not considered potential comparators because their availability in the NHS in the future is not guaranteed. The committee concluded that the treatment pathway has changed rapidly and that this would be considered in the decision-making process.

Comparators

3.3 The committee noted that the treatment options for relapsed or refractory DLBCL after 2 previous systemic treatments depend on which treatments the person has had and whether CAR T-cell therapy is suitable. The company highlighted that loncastuximab tesirine would only be used when CAR T-cell therapy is not suitable. This means that the current available treatment options for this population at the time of this evaluation were:

- chemotherapy, including rituximab-based chemotherapy
- polatuzumab plus BR (see NICE's technology appraisal guidance on polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma)
- pixantrone (see NICE's technology appraisal guidance on pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphoma)

The company included polatuzumab plus BR and chemotherapy as comparators. The company did not consider pixantrone a relevant comparator because it is rarely used in clinical practice. Both the clinical experts and the NHS England CDF lead agreed that polatuzumab plus BR is a relevant comparator, although its use may decrease in the future. The clinical experts explained that chemotherapy is used less than other options at this stage of the pathway, but it is still a relevant comparator, and may be used more in the future. The EAG reported that clinical input indicated that loncastuximab tesirine might be used in people for whom CAR T-cell therapy is unsuitable. The committee concluded that although the pathway is quickly changing, the company's positioning is appropriate and both polatuzumab plus BR and chemotherapy are relevant comparators.

Clinical evidence

Indirect comparisons

3.4 Clinical evidence for loncastuximab tesirine came from LOTIS-2, a single-arm, phase 2 trial that collected data on 145 people with relapsed or refractory DLBCL, including HGBL, that had not responded to 2 or more previous systemic treatments. The primary outcome of overall response rate was 48%, and 25% of participants reached complete remission. Median overall survival was 9.5 months and median progression-free survival was 4.9 months. Because there was no evidence directly comparing loncastuximab tesirine with any of the comparator treatments, the company did matched-adjusted indirect treatment comparisons (MAICs) against each of the comparators.

3.5 To compare loncastuximab tesirine with polatuzumab plus BR, the company used data from LOTIS-2 and GO29365, a single-arm extension study, which included 152 people with relapsed or refractory DLBCL after one or more treatments. The company based its matching on 7 baseline characteristics. The baseline characteristics were only available across the whole study population, so included data for people who only had one previous treatment. The company's results showed that loncastuximab tesirine had similar or slightly worse efficacy compared with polatuzumab plus BR. The exact results are considered confidential by the company and cannot be reported here. At technical engagement, the company provided 2 additional sensitivity analyses for the MAIC comparing loncastuximab tesirine and polatuzumab plus BR. One analysis excluded people if their disease response to primary therapy was missing, and the second analysis included matching against all available characteristics, including the International Prognostic Index (IPI). The results of these sensitivity analyses were similar to the base case analysis, suggesting a hazard ratio for overall survival close to 1 and a hazard ratio for progression-free survival favouring polatuzumab plus BR.

3.6 To compare loncastuximab tesirine with chemotherapy, the company used data from LOTIS-2 and CORAL, an extension study, which included 278 people. It based the matching on 3 baseline characteristics. The company's results showed that loncastuximab tesirine was better than chemotherapy at increasing how long people live with a hazard ratio of 0.67 for overall survival (95% confidence interval 0.51 to 0.86), and overall disease response, with a hazard ratio of 1.53 (95% confidence interval 0.91 to 2.54). Data on how long people live before their condition gets worse was not available for this comparison.

3.7 The EAG highlighted several concerns with the MAICs. The company based its preferred characteristics for matching on clinical opinion, but these characteristics were not available across all the key studies. Also, the company did not use age, Ann Arbor stage or Eastern Cooperative Oncology Group (ECOG) characteristics for matching in their base case analysis if the IPI stage was available, because these factors are already included in calculating the IPI stage. The EAG considered that all available characteristics should have been used. It also noted that the studies included in the MAICs had different sample sizes, and there were differences across study populations and study definitions. The EAG highlighted that for the comparison with polatuzumab plus BR, the company did not provide an analysis combining both sensitivity analyses, or Kaplan–Meier curves for the MAIC adjustments, and that the results of the sensitivity analyses were not used in the model. It also highlighted that the MAIC analyses results are similar to naive comparisons between the studies, which adds uncertainty to the benefit of using the MAIC analyses. The committee concluded that the results of the MAIC analyses were very uncertain.

Economic model

Company's model

3.8 The company used a partitioned survival model to estimate the cost effectiveness of loncastuximab tesirine. The model included 3 health

states: progression-free, progressed disease and death. The probability of staying in each health state was calculated using overall survival and progression-free survival curves. The committee concluded that the model was suitable for decision-making.

Overall survival and progression-free survival compared with polatuzumab plus BR

3.9 To estimate long-term overall survival and progression-free survival, the company fitted parametric models to the MAIC results. In its base case, the company applied a generalised gamma extrapolation for loncastuximab tesirine for both overall survival and progression-free survival because it stated generalised gamma had the best fit to the data. For overall survival, the EAG considered that the log-normal extrapolation had a similar fit to the data, but the long-term predictions of survival were more plausible than with the generalised gamma extrapolation. The clinical experts advised that after 10 years, it was reasonable to assume around 5% of patients would still be alive. The company considers the extrapolated results to be confidential so they cannot be reported here. But the committee noted that the log-normal extrapolation predicted a 10-year overall survival closer to 5% than the generalised gamma extrapolation. It also did not consider it plausible that loncastuximab tesirine would significantly increase 10-year overall survival compared with current practice. For progression-free survival, the EAG noted that the generalised gamma extrapolation was more optimistic in the long-term than most of the other parametric models. Although it appeared similar to the Kaplan—Meier curve from LOTIS-2, there were very few patients remaining at risk in LOTIS-2 after 12 months, so it was very uncertain. Therefore, the EAG used the log-normal extrapolation in its base case model. The committee concluded that, for both overall survival and progression-free survival, the log-normal extrapolation was more plausible than the generalised gamma extrapolation.

3.10 To model overall survival and progression-free survival for polatuzumab plus BR after 2 or more treatments, rather than using the hazard ratios estimated by the MAIC analysis, the company extrapolated data from the GO29365 study and adjusted for the effect of including people who had polatuzumab plus BR as second-line treatment. The extrapolated curves showed that loncastuximab tesirine had better overall survival and progression-free survival than polatuzumab plus BR. The EAG considered this implausible because the MAICs showed similar efficacy between loncastuximab tesirine and polatuzumab plus BR. In its base case, the EAG set overall survival and progression-free survival for polatuzumab plus BR equal to that of loncastuximab tesirine. The committee noted that most of the benefit in progression-free survival for loncastuximab tesirine was shown in the extrapolated period outside of the trial. Clinical experts advised that most of the benefit, and whether the disease would relapse or progress, would likely be seen in the first 2 years of treatment. The committee agreed that, given the MAIC results, assuming equivalent overall survival and progression-free survival between loncastuximab tesirine was most plausible.

Overall survival compared with chemotherapy

3.11 To model overall survival for chemotherapy, the company applied a hazard ratio from the MAIC analysis to its generalised gamma extrapolation for loncastuximab tesirine. The EAG advised that the generalised gamma extrapolation could be implausibly optimistic as it is affected by background mortality restrictions and preferred to apply a log-normal extrapolation. The committee concluded that the log-normal extrapolation was the most plausible.

Rates of subsequent autologous stem cell transplantation

3.12 For the comparison with chemotherapy, the company used data from the CORAL extension study to inform the rate of subsequent autologous stem cell transplantation following chemotherapy. In its base case, 22% of people had an autologous stem cell transplant after chemotherapy, and

3% after loncastuximab tesirine. The EAG considered that the rate of subsequent autologous stem cell transplantation after chemotherapy was highly uncertain. So, in its base case model, it included a rate of 3% after both chemotherapy and loncastuximab tesirine and provided scenario analyses to explore different rates. Clinical experts agreed that the rates reported by CORAL were higher than they would expect to see in clinical practice. The company stated that changing the rate for autologous transplantation after chemotherapy to match the loncastuximab tesirine arm would not be reflective of the CORAL study. It stated that this would result in bias by retaining the efficacy of the CORAL study but without updating the costs to align with the new rate. The committee concluded the rate of autologous stem cell transplantation after chemotherapy was uncertain and that it could be as low as 3%, but that changing it did not have a large impact on the cost-effectiveness results.

Severity

3.13 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight, called a severity modifier, to quality-adjusted life years (QALYs) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. The company and EAG agreed that for the comparison with chemotherapy, the QALYs should have a higher weighting of 1.2 because of the severity of the condition. The company and EAG agreed that for the comparison with polatuzumab plus BR, the severity weighting did not apply. So, the committee concluded that applying the severity weighting of 1.2 to the QALYs for the comparison with chemotherapy was appropriate.

Cost-effectiveness estimates

Acceptable incremental cost-effectiveness ratio (ICER)

3.14 NICE's manual on health technology evaluation notes that above a most plausible ICER of £20,000 per QALY gained, decisions about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the evidence presented, but will also consider other aspects including uncaptured health benefits. The committee agreed that the indirect treatment comparisons showed that loncastuximab tesirine was more effective than chemotherapy and had similar efficacy to polatuzumab plus BR. But there is considerable uncertainty because of the lack of direct evidence and concerns about the MAICs. So, the committee agreed that it would accept an ICER at the lower end of the acceptable range (less than £20,000).

Company and EAG cost-effectiveness estimates

3.15 There is a confidential commercial arrangement for loncastuximab tesirine and the comparators, so the exact cost-effectiveness estimates are confidential and cannot be reported here. The company and EAG base cases differed in 3 key areas, which were the key areas of remaining uncertainty:

- The long-term overall survival and progression-free survival with loncastuximab tesirine, for the comparison of loncastuximab tesirine and polatuzumab plus BR (see section 3.9). The company assumed generalised gamma extrapolation, and the EAG assumed log-normal extrapolation.

- The long-term overall survival and progression-free survival of polatuzumab plus BR (see section 3.10). The company generated a hazard ratio based on the GO29365 study, and the EAG

assumed polatuzumab plus BR overall survival and progression-free survival was the same as for loncastuximab tesirine.

- The long-term overall survival with loncastuximab tesirine, for the comparison of loncastuximab tesirine and chemotherapy (see section 3.11). The company assumed generalised gamma extrapolation, and the EAG assumed log-normal extrapolation.

The committee agreed that its preferred assumptions were those used in the EAG base case. It also agreed that the rate of subsequent autologous stem cell transplant after chemotherapy was uncertain but could be as low as 3% (see section 3.12). Compared with chemotherapy, the ICERs including the severity weighting were above £30,000 per QALY gained. Compared with polatuzumab plus BR, the committee preferred to assume no QALY difference between loncastuximab tesirine and polatuzumab plus BR, so only considered the difference in cost and loncastuximab tesirine was substantially more expensive than polatuzumab plus BR. The committee concluded that loncastuximab tesirine was not a cost-effective treatment option compared with the relevant comparators.

Managed access

3.16 Because the committee concluded that loncastuximab tesirine could not be recommended for routine use, the committee considered if it could be recommended with managed access for treating DLBCL and HGBL after 2 or more systemic treatments. The committee discussed the criteria for a managed access recommendation by NICE (see NICE's webpage on managed access). It noted that the company had not submitted a proposal for managed access. The committee was aware of an ongoing phase 3 trial for loncastuximab tesirine, but to evaluate loncastuximab tesirine in combination with rituximab after 1 or more previous treatments. The committee decided that the ongoing trial would not be able to resolve the uncertainties associated with the indirect treatment comparisons (see

section 3.4 to 3.7). So, the committee concluded that loncastuximab tesirine could not be recommended for managed access.

Other factors

Equality

3.17 The committee did not identify any equality issues.

Innovation

3.18 The committee considered if loncastuximab tesirine was innovative. It did not identify additional benefits of loncastuximab tesirine not captured in the economic modelling. So it concluded that all additional benefits of loncastuximab tesirine had already been taken into account.

Conclusion

3.19 Compared with chemotherapy, the most likely cost-effectiveness estimates for loncastuximab tesirine are above the range that NICE considers an acceptable use of NHS resources. Compared with polatuzumab plus BR, there was no QALY difference and loncastuximab tesirine was substantially more expensive than polatuzumab plus BR. So, the committee concluded not to recommended loncastuximab tesirine for routine use in the NHS for treating relapsed or refractory DLBCL and HGBL after 2 or more systemic treatments in adults.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Stephen O'Brien
Chair, technology appraisal committee C

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Lauren Elston
Technical lead

Alexandra Filby
Technical adviser

Louise Jafferally
Project manager

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