SMC2609

Loncastuximab tesirine solution for infusion (Zynlonta®)

Swedish Orphan Biovitrum (Sobi)

12 January 2024

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan equivalent medicine process

Loncastuximab tesirine (Zynlonta®) is accepted for restricted use within NHSScotland.

Indication under review: as monotherapy 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.

SMC restriction: where chimeric antigen receptor (CAR) T-cell therapy is unsuitable, not tolerated or ineffective.

In an open-label, single-arm, phase II study, in adults with relapsed or refractory DLBCL (which included HGBL) following two or more multi-agent systemic treatment regimens, Loncastuximab tesirine was associated with an overall response rate of 48%.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair,
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Loncastuximab tesirine is a CD19-targeted antibody drug conjugate. It is internalised following binding to CD19, a transmembrane protein expressed on the surface of cells of B-lineage origin. After internalisation the small molecule component, SG3199, an alkylating agent, is released via proteolytic cleavage and binds to the DNA, leading to cell death.[1]

The recommended dose of Loncastuximab tesirine is 0.15 mg/kg intravenously every 21 days for 2 cycles, followed by 0.075 mg/kg every 21 days for subsequent cycles until disease progression or unacceptable toxicity.[1]

1.2. Disease background

Diffuse Large B-cell Lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) are fast growing Non-Hodgkin's Lymphoma (NHL) originating from B cells. DLBCL represents a predominant subtype of NHL, constituting 25% to 45% of cases globally and encompassing 60% of new lymphoma diagnoses in the elderly. These aggressive diseases are often diagnosed in older adults. The majority of cases present at an advanced stage, and the prognosis of relapsed or refractory patients is extremely poor.[2-4]

1.3. Company proposed position

The submitting company requested that SMC consider Loncastuximab tesirine use where chimeric antigen receptor (CAR) T-cell therapy is unsuitable, not tolerated or ineffective.

1.4. Treatment pathway and relevant comparators

Clinical experts consulted by SMC considered that in the proposed positioning the predominant treatment option and most likely to be displaced by Loncastuximab tesirine is polatuzumab in combination with bendamustine and rituximab. Other potential treatment options include palliative care and chemotherapy (rituximab-gemcitabine-oxaliplatin [R-GemOx], rituximab-gemcitabine-cyclophosphamide-vincristine-prednisolone [R-Gem-CVP], cyclophosphamide-etoposide-procarbazine-prednisone [CEPP] or prednisolone-etoposide-lomustine-chlorambucil [PECC]) which can be poorly tolerated. Other options may include participation in clinical studies or, for selected patients, a stem-cell transplantation.[2, 5-7]

1.5. Category for decision-making process

Eligibility for interim acceptance decision option
Loncastuximab tesirine has conditional marketing authorisation from the Medicines and Healthcare Products Regulatory Agency.

Eligibility for a PACE meeting
Loncastuximab tesirine meets SMC end of life and orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of Loncastuximab tesirine for this indication comes from the open-label, single-arm, phase II study, LOTIS-2. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study

Criteria	LOTIS-2 [2, 8-10]
Study design	International, open-label, single-arm, phase II study
Eligible patients	The key inclusion criteria were: • ≥ 18 years. • Pathologic diagnosis of DLBCL, as defined by the 2016 World Health Organization (WHO) classification, to include: DLBCL not otherwise specified; primary mediastinal large B-cell lymphoma; and high-grade B-cell lymphoma, with myelocytomatosis and B-cell lymphoma 2 apoptosis regulator and/or B-cell lymphoma 6 transcription repressor rearrangements. • Relapsed or refractory disease following two or more multi-agent systemic treatment regimens. • Measurable disease as defined by the 2014 Lugano classification and availability of formalin-fixed paraffin-embedded tumour tissue block (or minimum 10 freshly cut unstained slides if block was not available). If several samples, the most recent was preferred. • Eastern Cooperative Oncology Group performance status 0 to 2.
Treatments	Patients received Loncastuximab tesirine as an intravenous infusion on day 1 of each 3-week cycle at a dose of 0.15 mg/kg for 2 cycles and then 0.075 mg/kg for subsequent cycles. Treatment was to continue for up to 1 year or until progressive disease, unacceptable toxicity, or other discontinuation criteria, whichever occurred first. Concomitant oral dexamethasone (4mg) was administered as pre-medication: one day before, on the day of, and the day after Loncastuximab tesirine administration.
Primary outcome	ORR defined as the proportion of patients with CR or PR according to the 2014 Lugano classification, determined by independent central review.
Selected secondary outcomes	• DOR defined as the time from the first documentation of tumour response to disease progression or death • CR rate defined as the percentage of treated patients with a BOR of CR • PFS defined as the time between start of treatment and the first documentation of recurrence, progression, or death • OS defined as the time between the start of treatment and death from any cause
Statistical analysis	Efficacy analyses were performed in the all-treated population, which included all patients who received at least one dose of Loncastuximab tesirine. Results are descriptive only.
Abbreviations: BOR, best overall response; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.	

At the final September 2022 data cut off, Loncastuximab tesirine was associated with an overall response rate (ORR) of 48%. Details of the primary and selected secondary outcomes have been presented in Table 2.2.

Table 2.2: Primary and selected secondary outcome results final September 2022 data cut off [8]

	Loncastuximab tesirine (n=145)
ORR, % (95 % CI)	48% (40 to 57)
CR, %	25%
PR, %	23%
Median DOR (months), 95% CI	13 (6.9 to NR)
KM DOR estimate at 24 months, 95% CI	45 % (28 to 60)
Median PFS, 95% CI	4.9 months (2.9 to 8.3)
KM PFS estimate at 24 months, 95% CI	26% (16 to 37)
Median OS, 95% CI	9.5 months (6.7 to 11.5)
KM OS estimate at 24 months, 95% CI	30 % (22 to 37)
Abbreviations: CI, confidence interval; CR, complete response; DOR, duration of response; KM, Kaplan–Meier; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.	

2.2. Evidence to support the positioning proposed by the submitting company

Among the 9.7% of patients who were previously treated with CAR T-cell therapy, Loncastuximab tesirine was associated with an ORR of 43 %.[8]

2.3. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed using EuroQol–5 Dimensions–5 Levels (EQ-5D-5L) and Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym). FACT-Lym is a lymphoma-specific subscale for the Functional Assessment of Cancer Therapy (FACT) questionnaire. It consists of 15 specific items that are used together with the core 27-item questionnaire FACT-G (a higher score indicates a worse level of QoL).[9]

The mean EQ-5D-5L change in visual analogue score (VAS) showed a trend of improvement in overall health over time. Mean changes in FACT-Lym subscale and composite scores were generally stable over time.[2]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence versus relevant comparators, the submitting company performed matching adjusted indirect comparisons (MAICs) to compare Loncastuximab tesirine versus comparators for the treatment of relapsed or refractory DLBCL and HGBL, after two or more lines of systemic therapy. The MAIC against polatuzumab with bendamustine plus rituximab, which informed the economic base case, compared pooled individual patient data from LOTIS-2 for Loncastuximab tesirine with an extension cohort from study GO29365 for polatuzumab with bendamustine plus rituximab. To inform a scenario analysis in the economic case, LOTIS-2 individual patient data were also compared with real-world data for polatuzumab with bendamustine plus rituximab from the COTA US database. Efficacy outcomes for overall survival (OS), progression free survival (PFS) and ORR were compared for Loncastuximab tesirine versus polatuzumab with bendamustine plus rituximab. Safety outcomes assessed were discontinuation due to adverse event (AE), grade 3-4 AE, and serious AE of any grade. A separate MAIC, the results of which were used in a sensitivity analysis in the economic case, was also conducted against chemotherapy and used an extension to the CORAL study (for chemotherapy).[11-15] Efficacy outcomes for OS and ORR were compared for Loncastuximab tesirine versus chemotherapy.

Table 2.3. Summary of indirect treatment comparison

Criteria	Overview
Design	Unanchored MAICs
Population	Adult patients with relapsed or refractory DLBCL and HGBL, after two or more lines of systemic therapy
Comparators	Polatuzumab with bendamustine plus rituximab. Chemotherapy (including rituximab, ifosfamide, carboplatin and etoposide [R-ICE]; rituximab, dexamethasone, high-dose cytarabine and cisplatin [R-DHAP] or gemcitabine-containing regimens, cyclophosphamide, doxorubicin, vincristine and prednisone [CHOP]-like regimens) was included in a separate MAIC (results only used in a sensitivity analysis).
Studies included	Pooled individual patient data from LOTIS-2 (for Loncastuximab tesirine), an extension cohort from study GO29365 and real-world data from the COTA US database (for polatuzumab with bendamustine plus rituximab), and an extension to the CORAL study (for chemotherapy).[11-15]
Outcomes	MAICs against polatuzumab with bendamustine plus rituximab: OS, PFS, ORR and safety outcomes (discontinuation due to AE, grade 3-4 AE, and serious AE any grade) MAIC against chemotherapy: OS and ORR
Results	Results suggest similar efficacy between Loncastuximab tesirine and polatuzumab with bendamustine plus rituximab for all efficacy outcomes, with all hazard ratios and odds ratios 95% CIs crossing 1. The comparison between Loncastuximab tesirine and polatuzumab with bendamustine plus rituximab for safety outcomes comes from LOTIS-2 and the G029365 extension study respectively.[11, 13] For Loncastuximab tesirine versus polatuzumab with bendamustine plus rituximab, the company found a significantly lower odds of grade 3-4 infections and infestations, and a significantly lower odds of any serious AEs; reductions in risk were seen in febrile neutropenia, pyrexia and fatal AEs. For the comparison against chemotherapy, results suggest Loncastuximab tesirine had a greater median OS (10.1 months [95% CI 6.3 to 13.6] versus 5.9 months [95% CI 4.8 to 7.1]) with a hazard ratio of 0.7 (95% CI 0.5 to 0.9) and greater ORR (51% versus 40%) with an odds ratio of 1.5 (95% CI 0.9 to 2.5).

Abbreviations: AE, adverse event; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; ESS, effective sample size; HGBL, high-grade B-cell lymphoma; MAIC, matching adjusted indirect comparison; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

3. Summary of Safety Evidence

Regulators concluded that the toxicity pattern of Loncastuximab tesirine seems acceptable and in line with other antibody-drug conjugates. The most common adverse reactions are oedema/effusions, gastrointestinal and haematological toxicity. The current safety database was considered acceptable for a conditional marketing authorisation and the confirmatory phase III study (in combination with rituximab) may help confirm the safety profile.[2]

In LOTIS-2 at the final data cut-off, the median duration of treatment was 45 days (range: 1 to 569) and the median number of treatment cycles was 3 (range: 1 to 26). Any treatment-emergent

adverse event (AE) was reported by 99% (143/145) of patients. Patients reporting a grade 3 or higher AE were 74%, and patients discontinuing therapy due to an AE was 25%.[8]

The most frequently reported treatment-emergent AEs with grade ≥3 with an incidence >10% were: neutropenia (26%), thrombocytopenia (18%), increased gamma-glutamyl transferase (17%), and anaemia (10%).[8]

No deaths due to treatment emergent AEs were considered to be related to treatment.[8]

In LOTIS-2, no patients tested positive for antibodies against Loncastuximab tesirine after treatment. [1]

4. Summary of Clinical Effectiveness Considerations

The key strengths and uncertainties of the clinical case are summarised below.

4.1. Key strengths

- ORR results were considered encouraging and clinically meaningful in a heavily pre-treated population of patients with relapsed or refractory DLBCL who had received two or more prior lines of systemic therapy (43% of the patients received two prior therapies, 24% received three prior therapies and 32% received more than three prior therapies).[2]
- The median duration of response was also considered clinically meaningful.[2]

4.2. Key uncertainties

- Key clinical data are from an open-label, single arm, phase II study with a short follow-up duration. The lack of control impacts the robustness and interpretation of the efficacy and safety data. In addition, with the open-label design, there is a potential for bias in the assessment of some outcomes, which could affect the reliability of the study findings. Regulators noted that the open-label nature of the study was acceptable considering the rarity and prognosis of this clinical setting. However, while recognising that there was no standard of care at that time, they considered that a randomised controlled study would have been preferred with investigator choice as comparator. Regulators concluded that the lack of control and the short follow-up duration may restrict the interpretation and extrapolation of the data.[2]
- Direct comparative data against any potentially relevant comparator are lacking. It should be noted that treatment in the proposed positioning may change with time, especially as polatuzumab has recently been accepted for restricted use in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone, for the treatment of adult patients with previously untreated DLBCL (restricted in patients with an International Prognostic Index score of 2 to 5), thus polatuzumab use in later lines may decrease.
- In the absence of direct data, the submitting company performed unanchored MAICs in patients with relapsed or refractory DLBCL and HGBL, after two or more lines of systemic therapy to compare Loncastuximab tesirine to polatuzumab with bendamustine plus rituximab.[11-13] Several limitations affect the results and conclusions of these MAICs including: the comparisons were all unanchored and consisted of a small number of studies, including single arm ones and real-world data; the extension cohort of study G029365 included patients

who failed at least one prior systemic therapy; data were available for third and later lines however the baseline characteristics were pooled for the entire population and not available in the relevant subgroups; not all prognostic or effect modifying factors were adjusted for within each comparison and the definition of relapsed and refractory disease differed between trials making it impossible to adjust for; and confidence intervals were wide. The separate comparison against chemotherapy only informed a sensitivity analysis. The results should be reviewed with caution due to limited evidence and limited availability of baseline characteristics, making matching across variables difficult. Due to the identified limitations, the indirect comparison results are highly uncertain.

- The study population was wider than the proposed positioning. The submitting company noted it is unknown how many patients in LOTIS-2 were unsuitable for CAR T-cell therapy or did not tolerate it and no data are available in the overall subgroup relevant to the proposed positioning (that is patients where CAR T-cell therapy is unsuitable, not tolerated or ineffective). The company noted that LOTIS-2 began recruiting in 2018, ahead of the availability of CAR T-cell therapies in some cases. Although exploratory subgroup data are to be interpreted with caution, among the 9.7% of patients who were previously treated with CAR T-cell therapy, results seem consistent with the overall study population.
- In LOTIS-2, 16 patients received CAR T-cell therapy at some time after progression following Loncastuximab tesirine therapy. Of these, 10 died at some time after CAR T-cell therapy (nine due to disease progression and one due to other reasons). Regulators noted although Loncastuximab tesirine may facilitate bridging to CAR T-cell treatment, efficacy and safety of this treatment after Loncastuximab tesirine needs further exploration. [2]

4.3. GB conditional marketing authorisation specific obligations

In the context of the conditional marketing authorisation, results from a phase III, controlled, randomised study, ADCT-402-311, of Loncastuximab tesirine combined with rituximab versus standard immunochemotherapy (rituximab / gemcitabine / oxaliplatin) in patients with relapsed or refractory DLBCL, are to be submitted by end 2025 to confirm the efficacy and safety in the licensed indication.[2, 16]

The MHRA specific obligations are unlikely to address the key uncertainties in the clinical evidence presented for this indication, as this will not provide data for Loncastuximab tesirine monotherapy.

4.4. Clinical expert input

Clinical experts consulted by SMC considered that Loncastuximab tesirine fills an unmet need and is a therapeutic advancement for this patient population with very few treatments options and poor outcomes.

4.5. Service implications

Clinical experts consulted by SMC generally considered that there would be no significant service implications associated with the introduction of Loncastuximab tesirine.

5. Summary of Patient and Carer Involvement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **Loncastuximab tesirine**, as an **orphan-equivalent and end of life** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Relapsed/refractory DLBCL/HGBL often present as rapidly progressive and devastating conditions, requiring frequent hospital visits even with only best supportive care.
- Currently, there is a lack of treatment options for patients ineligible for CAR T-cell therapy or who are experiencing relapse post-treatment, resulting in a very poor prognosis.
- This medicine with a different mode of action holds the potential to make a substantial impact on health-related benefits. Patients who respond may potentially benefit from a prolonged life with a good quality of life.
- This easily administered treatment is anticipated to reduce the necessity for frequent hospital visits, proving advantageous for patients, families, and caregivers. This, in turn, may help minimise the psychological impact of isolation, preserve independence, alleviate emotional strain, and enhance overall quality of life, allowing for increased meaningful time spent with loved ones. Its straightforward administration is not expected to burden already stretched healthcare services.
- Generally well-tolerated, Loncastuximab tesirine has a slightly unusual side effect profile, including rash, often photosensitive, and oedema; however these are considered manageable with appropriate counselling.
- With the approval of polatuzumab in the first line, the use of polatuzumab with bendamustine plus rituximab is likely to diminish in later lines. This novel medication provides a more viable option for patients unable to tolerate or who have previously undergone polatuzumab therapy.

Additional Patient and Carer Involvement

We received a patient group submission from Lymphoma Action, which is a registered charity. Lymphoma Action has received 6.7% pharmaceutical company funding in the past two years, with none from the submitting company. A representative from Lymphoma Action participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as described in Table 6.1

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	The company submitted a cost-utility analysis. Due to the results of the indirect comparison, the SMC also considered the results of a cost-minimisation analysis.
Time horizon	Lifetime (40 years based on an assumed starting age of 62.7 years)
Population	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.
Comparators	Loncastuximab tesirine was compared with polatuzumab with bendamustine plus rituximab (pola+BR).
Model description	A partitioned survival analysis with three health states (progression-free, progressed disease, and death).
Clinical data	The primary source of clinical data was the single arm study LOTIS-2, which informed outcomes for Loncastuximab tesirine.[2] The full study sample was used to estimate PFS, OS and time to treatment discontinuation (TTD). The PFS and OS for pola+BR patients were estimated by digitising the Kaplan Meier curves reported from the GO29365 extension study.[13] Both sets of data were subject to adjustment. LOTIS-2 data was reweighted based on the weights estimated within the MAIC analysis. The GO29365 study population contained second line patients as well as those on third line treatment. The Kaplan Meier curves were not reported separately based on treatment stage. The company estimated a hazard ratio between second line and third line patients, and used that to estimate survival for an exclusively third line population.
Extrapolation	Independent parametric survival functions were applied in order to extrapolate PFS, OS and TTD for Loncastuximab tesirine and the pola+BR arm. The process of selecting the most appropriate parametric model was assessed using goodness-of-fit statistics, visual comparison with Kaplan Meier curves, and clinical expert validation of long-term extrapolations and the underlying hazard functions. The generalised gamma curve was selected to extrapolate OS, PFS and TTD for Loncastuximab tesirine and pola+BR, with alternative distributions tested in scenario analysis.
Quality of life	Utility values were based on EQ-5D-5L data from the LOTIS-2 study, which were mapped onto the EQ-5D-3L. The base case utility values was 0.685 for the progression free state. Upon progression a further disutility of -0.056 was applied. A one-off adverse event disutility was applied in each arm.
Costs and resource use	The economic analysis included costs associated with medicine acquisition, administration, health-state monitoring, subsequent treatments, adverse events and terminal care.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price. The results presented do not take account of the PAS for polatuzumab but these were considered in the results used for decision-making. SMC is unable to

	present the results provided by the company which used an estimate of the PAS price for polatuzumab due to commercial confidentiality and competition law issues.

6.2. Results

The base case analysis presented by the submitting company, which included the PAS discount on Loncastuximab tesirine but not polatuzumab, indicated that Loncastuximab tesirine was dominant compared to polatuzumab with bendamustine plus rituximab. This meant it was estimated as resulting in lower costs and better health outcomes for patients.

*Other data were also assessed but remain confidential.**

6.3. Sensitivity analyses

In deterministic one-way sensitivity analysis, the parameters with the greatest impact on ICER were the GO29365 weights for PFS and the LOTIS-2 progression disutility. A range of scenario analyses were performed and presented in Table 6.3. These are inclusive of the PAS discount on Loncastuximab tesirine but not polatuzumab.

Table 6.3 Scenario analysis (PAS Price on Loncastuximab tesirine only)

Loncastuximab	**Scenario description**	**Base case description**	**ICER (£/QALY)**
1	1.5% discount rates	3.5% discount rates	Dominant
2	Comparator = Chemotherapy	Comparator = Pola+BR	£19,758
3	COTA study data for Pola+BR	G029635 study data for Pola+BR	Dominant
4	Gompertz for OS	OS, PFS and TTD extrapolated using the Generalised Gamma Curve for both arms	Dominant
5	Log-normal for OS		Dominant
6	Log-normal for PFS		SW: £2,008,637
7	Log-normal for OS and PFS		Dominant
8	Cure assumption at 2 years	No cure assumption	Dominant
9	Cure assumption at 5 years		Dominant
10	Cure assumption at 10 years		Dominant
11	10-year time horizon	40-year time horizon	Dominant
12	20-year time horizon		Dominant
13	Cost minimisation analysis – equal efficacy across Loncastuximab and Pola+BR	Cost utility analysis – differing efficacy across Loncastuximab and Pola+BR	Cost saving

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; Pola+BR, polatuzumab with bendamustine plus rituximab; OS, overall survival; PFS, Progression-free survival; SW, the estimated result sits in the South-West quadrant of the cost-effectiveness plane meaning the assessed medicine had lower costs and lower health outcomes than the comparator.
Notes: Dominant – In some scenarios Loncastuximab tesirine was dominant over pola+BR meaning it was estimated as resulting in lower costs and better health outcomes for patients.

6.4. Key strengths

The strengths in the model included the following:

- The selected comparator appeared to be the most likely medicine to be displaced in Scottish clinical practice. For additional context, the company provided an additional scenario using chemotherapy as the comparator (See Scenario 2, Table 6.3).
- The economic model is structurally sound and costing has been comprehensive.

6.5. Key uncertainties

The uncertainties in the model included the following:

- The economic modelling drew data for Loncastuximab tesirine patients from the full study population of LOTIS-2, containing patients who would have been suitable for CAR-T therapy. While some exploratory subgroup analysis suggested consistent effect across suitable and unsuitable subgroups, this introduces some uncertainty into the scale of the treatment effect for Loncastuximab tesirine projected within the model.
- There is no direct comparative evidence available comparing Loncastuximab tesirine against polatuzumab with bendamustine plus rituximab, which was considered the central comparator. The company performed an exploratory MAIC, and while those results were not used directly in the model, the weighting variables from that MAIC were applied to the data from the LOTIS-2 study. The MAIC was seen as a source of uncertainty and the decision to use the estimated weights introduced uncertainty into the model.
- The results of the central MAIC presented by the company, using the GO29365 data, showed no statistical difference in PFS or OS between Loncastuximab tesirine and polatuzumab with bendamustine plus rituximab. There was a small numerical benefit in PFS estimated for treatment with polatuzumab. The company attributed this to the presence of second line patients, who may be easier to treat, in the GO29365 study. After adjustment with a hazard ratio the economic model suggested PFS benefits for Loncastuximab tesirine patients. Given the results of the MAIC, the SMC considered that a cost-minimisation analysis may be appropriate. The cost-minimisation analysis provided by the company suggests that even if there were no differences in treatment effect, Loncastuximab tesirine would still be cost-saving compared to polatuzumab with bendamustine plus rituximab, although this did not take into account the PAS discount on polatuzumab (See Scenario 13, in Table 6.3).

7. Conclusion

The Committee considered the benefits of Loncastuximab tesirine in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as Loncastuximab tesirine is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted Loncastuximab tesirine for restricted use in NHSScotland.

8. Guidelines and Protocols

The European Society for Medical Oncology published in August 2015 'Recommended treatment strategies in diffuse large B-cell lymphoma >2 relapse/progress'.[7]

The British Society for Haematology published in May 2016 "Management of Diffuse Large B-cell Lymphoma".[6]

The National Institute for Health and Care Excellence published in July 2016 "Non-Hodgkin's lymphoma: diagnosis and management'.[5]

The National Comprehensive Cancer Network (NCCN) published in July 2023: NCCN Clinical Practice Guidelines in Oncology - B-Cell Lymphomas, Version 5.2023.[17]

9. Additional Information

9.1. Product availability date

21 December 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per cycle (£)
Loncastuximab tesirine	**0.15 mg/kg every 21 days for 2 cycles, followed by 0.075 mg/kg every 21 days**	**First 2 cycles: £30,400 Subsequent cycle: £15,200**

Costs from company's submission. Costs calculated using bodyweight of 70kg for an adult and the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The company estimates that there will be around 61 patients eligible for treatment with Loncastuximab tesirine each year. The uptake rate was estimated to be 10% in year one (6 patients) and 60% in year five (37 patients).

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 17 November 2023

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.