# NCPE Assessment

# Technical Summary

## Axicabtagene ciloleucel (Yescarta ®)

## 22066

16/10/2024

Applicant: Kite, a Gilead company

Axicabtagene ciloleucel is indicated for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) and high grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first line chemoimmunotherapy.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of axicabtagene ciloleucel (Yescarta ®).

Following assessment of the Applicant's submission, the NCPE recommends that axicabtagene ciloleucel (Yescarta ®) not be considered for reimbursement for this indication, unless cost-effectiveness can be improved relative to existing treatments.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Kite, a Gilead company) Health Technology Assessment of axicabtagene ciloleucel (Yescarta ®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

**About the National Centre for Pharmacoeconomics**

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

## Summary

In September 2023, Kite, a Gilead company submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of axicabtagene ciloleucel (Yescarta ®) for the treatment of adult patients with DLBCL and HGBL that relapses within 12 months from completion of, or is refractory to, first line chemoimmunotherapy. Kite, a Gilead company, is seeking reimbursement of axicabtagene ciloleucel on the Oncology Drugs Management System.

Axicabtagene ciloleucel is an autologous anti-CD19 CAR T-cell therapy. It is administered as a once-off, single-dose intravenous infusion in a qualified treatment centre. Prior to infusion, a patient may undergo a number of steps: leukapheresis, bridging therapy, and lymphodepleting therapy. Post-infusion monitoring should occur daily for the first 7 days after infusion, in a qualified treatment centre. Patients should remain within proximity of a qualified treatment centre for up to four weeks post-infusion.

According to the Applicant, the proposed place in therapy of axicabtagene ciloleucel is for the treatment of adult patients with DLBCL and HGBL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy who are intended for transplant. The clinical evidence and cost-effectiveness analysis presented by the Applicant in the HTA submission considers only this sub-population, which is narrower than that of the product licence. The comparator in the Applicant's submission is standard of care (salvage chemotherapy followed by high dose therapy and autologous stem cell transplant (HDT-auto-SCT)). The Review Group highlight that restricting the use of axicabtagene ciloleucel based on clinical and patient specific reimbursement criteria for HDT-auto-SCT would not be feasible given there is no universally accepted criteria for determining eligibility for transplant in the second-line setting. Clinical opinion indicates that some patients who are not considered for transplant due to age (greater than 70 years) may be considered eligible for axicabtagene ciloleucel in the second-line setting.

## 1. Comparative effectiveness of axicabtagene ciloleucel

### ZUMA-7

The efficacy and safety of axicabtagene ciloleucel was evaluated in the ZUMA-7 trial. This is a phase III global (77 sites worldwide), multicentre, randomised, open-label, parallel assignment trial evaluating the efficacy and safety of axicabtagene ciloleucel versus standard of care (SoC) in adult patients (n=359) with large B-cell lymphoma (DLBCL/HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy, and who are intended to proceed to HDT-auto-SCT. Frontline chemotherapy consisted of an anti-CD20 monoclonal antibody and anthracycline containing regimen. Primary refractory disease was defined in the trial protocol as no complete response (CR) to frontline chemoimmunotherapy, and relapse was defined as relapse from CR within 12 months of frontline chemoimmunotherapy. SoC was defined as salvage chemotherapy regimen selected by the investigator (including rituximab with ifosfamide, carboplatin, etoposide [R-ICE], rituximab with methylprednisolone, etoposide, cisplatin, cytarabine [R-ESHAP], rituximab with gemcitabine, dexamethasone, cisplatin [R-GDP], rituximab with cisplatin, cytarabine, dexamethasone [R-DHAP], or rituximab with dexamethasone, cytarabine, and oxaliplatin [R-DHAX]). Patients who demonstrated at least a partial response to salvage chemotherapy proceeded to HDT-auto-SCT. Axicabtagene ciloleucel was administered as a single intravenous infusion at a target dose of $2 \times 10^6$ anti-CD19 CAR T-cells/kg (minimum of $1 \times 10^6$ anti-CD19 CAR T-cells/kg. For patients weighing more than 100 kg, a maximum flat dose at $2 \times 10^8$ anti-CD19 CAR T-cells was administered. Bridging therapy with corticosteroids was allowed prior to lymphodepleting chemotherapy at the discretion of the investigator, prior to axicabtagene ciloleucel infusion.

Efficacy analyses were conducted according to the intention-to-treat principle and included all the patients who underwent randomization. The primary endpoint was event-free survival (EFS) as determined by blinded central assessment. EFS was defined as the time from randomisation to the earliest date of disease progression, starting a new lymphoma therapy (NALT), death from any cause or best response of stable disease up to and including response on the Day 150 assessment after randomisation. Key secondary endpoints were objective response rate (ORR) and overall survival (OS). The median study duration was 24.9

months at the time of the primary EFS analysis and 47.2 months at the time of the primary OS analysis.

At the time of the primary EFS analysis, axicabtagene ciloleucel was superior to SoC with respect to the primary endpoint; median EFS by blinded central assessment was longer in the axicabtagene ciloleucel arm (8.3 months; 95% confidence interval [CI], 4.5 to 15.8) compared with 2.0 months (95% CI, 1.6 to 2.8) in the SoC arm (hazard ratio (HR): 0.40 (95% CI 0.31 to 0.51, p <0.001)). The estimated EFS at 24 months was 41% (95% CI: 33% to 48%) compared with 16% (95% CI 11% to 22%) in the SoC arm. Axicabtagene ciloleucel also demonstrated improvement in ORR; ORR rates of 83% in the axicabtagene ciloleucel arm and 50% in the SoC arm. At the time of the primary OS analysis, a statistically significant improvement in OS in favour of axicabtagene ciloleucel was demonstrated; HR: 0.73 (95% CI 0.54 to 0.98, p=0.03). The estimated 48-month OS rates were 54.6% in the axicabtagene ciloleucel arm and 46.0% in the SoC.

As ZUMA-7 was an open-label trial, the investigator and patient decisions to initiate NALT in the SoC arm may have been influenced by knowledge of assigned treatment. The key driver of EFS benefit for axicabtagene ciloleucel was the larger proportion of NALT events in the SoC arm; initiation of NALT made up 44% (n=63/144) of all EFS events in the SoC arm. For all of these events, initiation of NALT occurred prior to (centrally-assessed) disease progression, and in the absence of 'best response of stable disease up to Day 150 assessment.' A large number of NALT events in the SoC arm (n=35/63) also occurred either in responding patients, patients who had stable disease following only 1 cycle of salvage chemotherapy, or patients who did not receive randomised treatment at all. As these events may not represent actual 'treatment failures', it is possible that the magnitude of the treatment effect of axicabtagene ciloleucel versus SoC on EFS is overestimated substantially. These events are expected to bias the EFS endpoint in favour of axicabtagene ciloleucel. The use of alternative EFS definitions that do not include 'early' NALT initiation as an event was not possible since no disease assessments were conducted following initiation of NALT. High rates of 'early' NALT initiation in the SoC arm may also be a source of bias in OS estimates.

## 2. Safety of axicabtagene ciloleucel

A total of 338 patients were included in the safety analysis set (SAS) from the primary analysis of EFS (18 March 2021). The SAS was defined as all randomised patients who received at least one dose of axicabtagene ciloleucel or re-induction therapy (axicabtagene ciloleucel arm n=170; SoC arm n=168). All patients had at least one adverse event (AE) of any grade. AEs of grade ≥3 occurred in 155 of 170 patients (91%) who received axicabtagene ciloleucel and in 140 of 168 patients (83%) who received SoC. The most commonly reported AE of grade ≥3 severity were neutropenia (69% versus 41%), anaemia (30% versus 39%), leukopenia (29% versus 22%), thrombocytopenia (15% versus 57%) in the axicabtagene ciloleucel arm versus SoC arms respectively. The safety profile of axicabtagene ciloleucel, observed in ZUMA-7, was consistent with the safety profile of axicabtagene ciloleucel in the third line relapsed or refractory DLBCL setting; ZUMA-1. There is a clear risk management plan available to support clinicians for monitoring for signs and symptoms of potential cytokine release syndrome (CRS), neurologic events and other toxicities as outlined in the summary of product characteristics.

## 3. Cost effectiveness of axicabtagene ciloleucel

*Methods*

A de novo model was developed using a partitioned survival analysis framework. The model structure comprised three health states (event-free, post-event, and death). To account for differences in the costs and health effects accrued by patients, the event-free state was subdivided into 'on treatment' and 'off treatment' sub-states. The post-event state was partitioned into on- and off-next treatment sub-states using parametric extrapolations of time-to next treatment (TTNT) curves from ZUMA-7, in order to determine post-event treatment costs. Treatment group-specific parametric mixture-cure models (MCM) were fitted to time-to-event data from ZUMA-7 to extrapolate EFS and OS, to the model's time horizon. The MCM splits the overall population into those who are cured of their disease and those who are not cured of their disease. All patients who remain alive and event-free at 5 years in the model are assumed to have quality-of-life equivalent to that of the age- and sex-matched general population, and incur limited monitoring costs, which is intended to reflect the assumption that these patients are effectively 'cured'. Clinical opinion obtained by both the Applicant and the Review Group agreed with the cure assumption. A key limitation of the

model structure was the inability to account for patients who achieve effective 'cure' from third or later line therapies, including CAR-T and stem-cell transplant. The model included drug acquisition, administration, monitoring, subsequent treatment, adverse event and end of life costs. Utility data were derived from EQ-5D-5L data collected during the ZUMA-7 and ZUMA-1 trials. Health state utility values were treatment-independent and disutilities associated with treatment and AEs were accounted for separately in the model.

The Review Group identified a number of limitations in the Applicant's base case, which were explored in the NCPE-adjusted base case. The choice of model used to extrapolate OS was considered to be highly uncertain, and an alternative was implemented by the NCPE. As many patients are expected to receive potentially curative therapies in third or later line settings, the NCPE also amended the model to allow for improved quality of life and reduced healthcare costs among those who may be considered 'cured' in later lines of therapy. Other changes made in the NCPE adjusted base case include the choice of model to extrapolate EFS, application of a utility decrement to 'cured' patients, and the inclusion of cryopreservation costs associated with axicabtagene ciloleucel.

### *Results*

The results of the Applicant's and NCPE adjusted base case deterministic cost-effectiveness analysis are presented in Tables 1 and 2.

**Table 1:Applicant base case incremental cost-effectiveness results [a]**

| Treatments | Total costs (€) | Total QALYs | Incremental costs (€) | Incremental QALYs | ICER (€/QALY) |
|---|---|---|---|---|---|
| SoC | €321,848 | 5.20 | - | - | - |
| Axi-cel[b] | €417,811 | 6.60 | €95,964 | 1.39 | 68,803 |

***SoC:*** *Standard of care;* ***Axi-cel:*** *Axicabtagene ciloleucel*

[a] Corresponding probabilistic ICER using 1,000 iterations =€72,331/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. The discount rate applied to costs and outcomes is 4%.
[b] A commercial in confidence Patient Access Scheme is in place for axicabtagene ciloleucel; not included in this table or these estimates.

**Table 2: NCPE adjusted base case incremental cost-effectiveness results [a]**

| Treatments | Total costs | Total | Incremental costs | Incremental | ICER |
|---|---|---|---|---|---|

| | (€) | QALYs | (€) | QALYs | (€/QALY) |
|---|---|---|---|---|---|
| SoC | 306,695 | 5.42 | | | |
| Axi-cel [b] | 409,323 | 6.44 | 102,628 | 1.01 | 101,256 |

***Axi-cel**; Axicabtagene ciloleucel; **SoC:** Standard of Care*

[a] Corresponding probabilistic ICER using 1,000 iterations =€107,996/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. The discount rate applied to costs and outcomes is 4%.

[b] A commercial in confidence Patient Access Scheme is in place for axicabtagene ciloleucel; not included in this table or these estimates

### *Sensitivity analysis*

Deterministic one-way sensitivity analysis indicated that the most influential parameters in the model for both the Applicant and the NCPE adjusted base case were the choice of MCM used to extrapolate OS and the corresponding MCM curve parameters, the proportions of patients receiving CAR-T in the third line or later setting, and the multiplier for excess mortality applied to 'cured' patients. A price-ICER analysis, using the NCPE-adjusted base case, indicated that a 61.4% and 45.1% reduction in the price-to-wholesaler of axicabtagene ciloleucel was required to meet the €20,000 per QALY and €45,000 per QALY thresholds, respectively.

## 4. Budget impact of axicabtagene ciloleucel

The price-to-wholesaler per single-dose intravenous infusion of axicabtagene ciloleucel is €322,251. The total cost to the HSE, inclusive of rebate and VAT, is €368,977 (€294,860 excluding VAT).

The eligible population is defined by the Applicant as patients with primary refractory or early relapsed DLBCL/HGBL, and who are intended to proceed to transplant; i.e. HDT-auto-SCT. This reflects the subpopulation of the licensed population that aligns with the patient population enrolled in the ZUMA-7 trial i.e., transplant eligible patients. Clinical opinion sought by the Review Group reported that criteria for determining fitness for axicabtagene ciloleucel or transplant are likely to align in clinical practice, however some patients who would be considered ineligible for transplant due to age restrictions may be considered for treatment with axicabtagene ciloleucel; specifically, those greater than 70 years. Following a request from the Review Group, the Applicant provided two models, one detailing the estimated drug budget impact associated with the treatment of the eligible population (full licenced population); and another detailing the estimated drug budget impact associated

with the treatment of the Applicant's requested sub-population (transplant eligible subpopulation). The Review Group consider that the estimates for the full licence population may be more reflective of clinical practice.

Based on population estimates obtained from the National Cancer Registry Ireland, the literature in this disease area, and clinical opinion, the Applicant estimates that in the full-licensed population, there will be 28 patients treated in year one, increasing to 37 by year five. In the transplant eligible subpopulation, the Applicant estimates there will be 15 patients treated in year one, increasing to 22 by year five. Based on the full-licensed population, the cumulative five-year gross and net drug budget impacts of axicabtagene ciloleucel, inclusive of VAT, were €56.60 million (€45.23 million excluding VAT) and €55.64 million (€44.44 million excluding VAT), respectively. In the transplant eligible subpopulation, the estimated five year cumulative gross drug budget impact of axicabtagene ciloleucel was €31.65 million (€25.29 million excluding VAT). The five-year cumulative net drug budget impact was €31.09 million (€24.84 million excluding VAT). The net budget impact estimates reflect drug costs only in the second line setting and do not account for costs or cost offsets associated with transplantation in the second line setting or subsequent treatments in the third line setting. The population of eligible patients and the proportion expected to receive treatment, are very uncertain. Therefore, there is considerable uncertainty associated with budget impact estimates.

## 5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

## 6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that axicabtagene ciloleucel (Yescarta ®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.*