**Cost effectiveness of axicabtagene ciloleucel (Yescarta®) for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.**

The NCPE have issued a recommendation regarding the cost effectiveness of axicabtagene ciloleucel (Yescarta®). Following assessment of the Applicant's submission, the NCPE recommend 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.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the Applicant's (Kite Gilead) economic dossier on the cost effectiveness of axicabtagene ciloleucel (Yescarta®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes 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 is 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.

**National Centre for Pharmacoeconomics** **February 2020**

**Summary**

In March 2019, Kite Gilead submitted a dossier of clinical, safety and economic evidence in support of axicabtagene ciloleucel (axi-cel) for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy. DLBCL arising from transformed follicular lymphoma (tFL) is covered by the licence. Final data submitted by the Applicant was received in December 2020.

Axi-cel is an advanced therapy medicinal product. It is a chimeric antigen receptor (CAR) T-cell therapy, which is manufactured using the patient's own T-cells. These T-cells are genetically engineered to express a CAR which binds to the CD19 antigen. Once axi-cel binds to the CD19-positive leukaemic cells, the CAR T-cell becomes activated and the cytotoxic action of these cells is initiated.

Axi-cel is administered as a once-off intravenous infusion in a specially accredited centre. Prior to infusion, a patient may undergo a number of steps: leukapheresis, bridging chemotherapy, and lymphodepleting chemotherapy. Post-infusion monitoring should occur daily for the first ten days, preferably in the inpatient setting, and patients should remain within the proximity of the hospital for up to four weeks post-infusion. Administration of axi-cel will require appropriately trained staff and immediate access to specialities such as intensive care and neurology.

In the submission, axi-cel was compared to a blended comparator consisting of GEM (gemcitabine and methylprednisolone), GEMOX (gemcitabine and oxaliplatin), R-ESHAP (rituximab, etoposide, methylprednisolone, high-dose cytarabine, cisplatin), and R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin). While the Review Group acknowledged that there is no universal standard of care for the indications in question, a blended comparator of R-GDP and R-GIFOX (rituximab, gemcitabine, ifosfamide, oxaliplatin) was employed in the NCPE adjusted analysis. This was adjusted following discussion with clinicians and to ensure consistency with previous assessments. In the absence of clinical data to inform the efficacy of comparator treatments, the SCHOLAR-1 data was employed as proxy data for the efficacy of these therapies. It was assumed that all comparator

treatments have equal efficacy. The Review Group acknowledged the paucity of data available. The lack of direct relative effectiveness data means that all relative efficacy and cost-effectiveness outputs must be interpreted with caution. The omission of tisagenlecleucel as a comparator was also highlighted as a limitation of the analysis.

1. **Comparative effectiveness of axicabtagene ciloleucel**

Clinical evidence for the approval of axi-cel comes from the ZUMA-1 trial.

ZUMA-1 was a phase I/II, single-arm, open-label, multicentre study evaluating the safety and efficacy of axi-cel in patients with chemotherapy-refractory DLBCL, PMBCL or transformed follicular lymphoma (ie DLBCL arising from follicular lymphoma; tFL). Patients must have received prior therapy with an anti-CD20 monoclonal antibody and an anthracycline-containing chemotherapy regimen. A total of 11 patients were screened during phase I. Of these, eight underwent leukapheresis and seven (of these eight) ultimately received infusion with axi-cel. In phase II, 124 patients were screened and 111 underwent leukapheresis. Of these, 101 (n=77 DLBCL; n=24 PMBCL/tFL) subsequently received infusion with axi-cel. Results were presented for the infused population only. The data used in the NCPE adjusted analysis were based on the phase II data, with a median follow-up of 27.1 months.

The primary endpoint of investigator-assessed objective response rate was 83%, with a complete response rate of 58%. Median progression-free survival was 5.9 months (95% CI 3.3 to 15.0), while median overall survival was not reached. A total of 50% of patients were alive at 24 months. The Review Group highlighted that the ZUMA-1 trial is subject to a number of limitations. The short follow up of the trial leads to uncertainty in determining how the survival data will develop over time. The open-label nature of the trial results in the potential for bias. The single-arm nature of the trial limits any conclusions that can be made regarding relative efficacy.

Estimates of relative efficacy versus comparator treatments were based on an unanchored indirect comparison method, known as standardised analysis, between the ZUMA-1 and the SCHOLAR-1 data. SCHOLAR-1 was an international, multicohort, retrospective study, evaluating overall survival in patients with refractory DLBCL and PMBCL (n=636). SCHOLAR-1

pooled data from the observational follow up of two phase II clinical trials (Lymphoma Academic Research Organisation-CORAL and Canadian Cancer Trials Group LY.12) and two observational cohorts (MD Anderson Cancer Centre and University of Iowa/Mayo Clinic Lymphoma Specialised Program of Research Excellence). The chemotherapy regimens received by patients in SCHOLAR-1 were not reported in the publication; however, clinical expertise obtained by the Review Group indicated that the treatments are likely to be in line with standard of care received in Ireland. Only overall survival data were available from SCHOLAR-1; progression-free survival was not recorded. The results of the standardised analysis, based on refractory subgroup and ECOG performance status, indicated that patients in ZUMA-1 had more favourable overall survival outcomes when compared to those in SCHOLAR-1. However, the Review Group did not consider heterogeneity between the trials to be appropriately addressed. Notably, ZUMA-1 had a higher proportion of patients with late-stage disease, patients aged 65 years and older and patients had received more prior lines of therapy. Thus, the magnitude of the true benefit of axi-cel relative to standard of care is unknown.

**2. Safety of axicabtagene ciloleucel**

All patients infused with axi-cel were included in the safety analysis of ZUMA-1.

Adverse events were experienced by 100% of patients in the phase II cohort of ZUMA-1. Adverse events of grade 3 or higher severity were experienced by 95% of patients. The most common adverse event was cytokine release syndrome (93%), with 13% of these experiencing cytokine release syndrome of grade 3 or higher severity. The most common symptoms of cytokine release syndrome of grade 3 or higher were pyrexia (11%), hypoxia (9%) and hypotension (9%).

Neurological events occurred in 64% of patients; 28% were grade 3 or higher severity. The most common neurological events of grade 3 or higher severity were encephalopathy (21%), confusional state (9%), aphasia (7%), and somnolence (7%).

Other frequently reported adverse events included: pyrexia (85%), neutropenia (84%), anaemia (66%), hypotension (59%), thrombocytopenia (48%), and nausea (58%).

The EMA Public Assessment Report has highlighted the risk of serious and life-threatening adverse events in patients treated with axi-cel. In order to address these risks, a number of risk minimisation measures have been put in place. Of note, the summary of product characteristics specifies that at least four doses of tocilizumab and emergency equipment must be available on-site for each patient (should it be required for the management of cytokine release syndrome). All health care professionals who are expected to prescribe, dispense, and administer axi-cel should undergo adequate training to facilitate identification and management of cytokine release syndrome and serious neurological adverse reactions.

## 3. Cost effectiveness of axicabtagene ciloleucel

For the cost-effectiveness analysis, the key effectiveness inputs were overall survival and progression-free survival. Clinical efficacy inputs were derived from ZUMA-1 and SCHOLAR-1. Cost effectiveness was based on a cost-utility partitioned survival model with a 44-year time horizon and a cycle length of one month. The model simulated patients through three health states: progression-free survival, progressed disease and death. All patients who received an infusion of axi-cel started in the progression-free survival state; transitions to death could occur from either the progression-free or progressed disease states.

Costs and health-related utilities were allocated to each health state. The model assumed that patients who remained in the progression-free survival health state after two years were subject to age- and gender-matched general population utility and incurred no further cancer-specific costs. This was not considered appropriate by the Review Group. Health-state utility values were derived from the ZUMA-1 trial. A once-off utility decrement for adverse events was applied at the start of the first cycle. This was applied to the axi-cel arm only. The cost components considered in the model included: pre-treatment cost, drug acquisition and administration costs, hospitalisation costs, adverse event costs, subsequent allogeneic stem cell transplant costs, follow-up and monitoring costs, and staff training costs. The Review Group updated a number of costs to reflect Irish-specific sources. Costs specific to axi-cel included: leukapheresis, lymphodepleting and bridging chemotherapy, treatment of cytokine release syndrome, and treatment of B-cell aplasia.

Survival outcomes from ZUMA-1 were extrapolated, to the full time horizon of the model, using a variety of extrapolation methods. The Applicant base case used the phase I/II data of ZUMA-1 and employed a Weibull mixture cure model for the extrapolation of overall survival. A Gompertz parametric curve was employed for the extrapolation of progression-free survival. The Review Group did not consider the follow-up of ZUMA-1 to be sufficiently long to support the use of a mixture cure model. The cure fraction estimated is unlikely to be robust and the risk of late relapse could not be excluded. In addition, the Review Group did not consider it appropriate to employ a mixture cure modelling approach to the extrapolation of overall survival but not progression-free survival. The implication of this approach is that patients can be cured in terms of survival but not in terms of progression. A standard parametric approach was employed to extrapolate the overall survival data of SCHOLAR-1. Progression-free survival data for SCHOLAR-1 were generated by assuming that the same ratio between progression-free survival and overall survival at each time point in the axi-cel arm can be applied to the comparator arm. In light of the paucity of data available, the Review Group considered this to be a reasonable approach to take. However, the Review Group highlighted that due to the different mechanisms of action, the relationship between progression-free survival and overall survival for the SCHOLAR-1 data may be different to that of axi-cel. The SCHOLAR-1 data were also adjusted to reflect the proportion of patients who are expected to receive a subsequent stem cell transplant in clinical practice.

A discount rate of 5% was employed for both costs and outcomes in the base-case analysis. A rate of 4% was explored in scenario analysis.

Analyses presented in this summary document are based on the list prices of interventions. The NCPE Review Group implemented a number of changes to the Applicant base case to reflect the most plausible assumptions. The most significant of these include: employing the phase II ZUMA-1 data for the axi-cel arm, and extrapolating the overall survival data of ZUMA-1 using a standard parametric approach. Based on these assumptions, axi-cel was associated with an ICER of €241,416 per QALY (incremental costs €417,349; incremental QALYs 1.73). The probability of cost effectiveness at a willingness-to-pay threshold of €45,000 per QALY was 0%.

The NCPE Review Group updated comparator costs in the Applicant base case to reflect Irish wholesale prices, in addition to dosing regimens used in the Irish setting; all other Applicant assumptions remained unchanged. Under these circumstances, the Applicant's assumptions generated an ICER of €87,957 per QALY (incremental costs €395,245; incremental QALYs 4.49). The probability of cost effectiveness at a willingness-to-pay threshold of €45,000 per QALY was 0%.

A number of scenario analyses were conducted to assess the impact of uncertainty associated with the structural and methodological assumptions. Scenarios pertaining to the time horizon had the greatest impact on the ICER. Assuming a two-year time horizon (the approximate follow-up of ZUMA-1), increased the NCPE Review Group adjusted analysis ICER to €982,241 per QALY (incremental costs €393,110; incremental QALYs 0.40). Although the Review Group acknowledge that this is a conservative assumption, it demonstrates the reliance of the model on the long-term extrapolation of survival outcomes.

## 4. Budget impact of axicabtagene ciloleucel

Axi-cel is submitted for reimbursement in the hospital setting. The proposed price to wholesaler per one-off infusion is €327,000. The total cost to the HSE, inclusive of rebate and VAT, is €384,225 (€309,015 excluding VAT).

The Applicant anticipates that one patient will be treated with axi-cel in year one, increasing to eight patients in year five. This is based on an estimated market share of 1% in year one, increasing to 19% in year five. The subsequent cumulative five-year gross budget impact is €9.2 million, accounting only for axi-cel acquisition costs. Taking procedure costs (leukapheresis, lymphodepleting chemotherapy) into account, the cumulative five-year gross budget impact increases to €10.5 million.

Based on the NCPE Review Group adjusted assumptions and assuming that 12 patients are treated in year one, with an additional 2 patients treated each year, the cumulative five-year gross budget impact is €30.7 million (€24.7 million excl. VAT) and €35.0 million (€28.9 million excl. VAT), when procedure costs are taken into account. This is based on the

assumption that increased experience in the administration of axi-cel will lead to an increase in the number of patients treated (to a maximum of 20 patients per year).

The cumulative five-year net budget impact of axi-cel (accounting for drug acquisition and procedure costs) is estimated to be between €9.9 million (€8.1 million excl. VAT) and €10.6 million (€8.6 million excl. VAT), depending on the number of patients treated. When additional costs (eg adverse event costs) and cost offsets are accounted for, the five-year net budget impact ranges between €10.9 million (€9.1 million excl. VAT) and €12.6 million (€10.5 million excl. VAT).

The NCPE Review Group highlighted the potential for a higher budget impact should the capacity to administer axi-cel in the Irish healthcare setting increase.

## 5. Patient submissions

No patient organisation submissions were received during this assessment.

## 6. Conclusion

Treatment with axi-cel is associated with particular institutional requirements, extremely high upfront costs and a limited evidence base. The HSE faces the possibility of large unrecoverable costs should this treatment not prove to be as effective as suggested by this highly uncertain effectiveness evaluation.

Following assessment of the Applicant's submission, the NCPE recommend that axicabtagene ciloleucel (Yescarta®) for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma, after two or more lines of systemic therapy not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments[i]*.

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