Cost-effectiveness of tisagenlecleucel (Kymriah®) for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

The NCPE has issued a recommendation regarding the cost-effectiveness of tisagenlecleucel (Kymriah®)**.** Following assessment of the Applicant's submission, the NCPE recommends that tisagenlecleucel (Kymriah®) 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 (Novartis Ireland Limited) economic dossier on the cost effectiveness of tisagenlecleucel (Kymriah®). 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 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.

National Centre for Pharmacoeconomics **September 2019**

Summary

In January 2019, Novartis Ireland Limited submitted a dossier of clinical, safety and economic evidence in support of tisagenlecleucel for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. Final data submitted by the Applicant was received in September 2019.

Tisagenlecleucel is the first advanced therapy medicinal product to be assessed by the NCPE. 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 tisagenlecleucel binds to the CD19 positive leukaemic cells, the CAR T-cell becomes activated and the cytotoxic action of these cells is initiated.

Tisagenlecleucel 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 proximity of the hospital for up to four weeks post-infusion. Administration of tisagenlecleucel will require appropriately trained staff and immediate access to specialities such as intensive care and neurology.

In the submission, tisagenlecleucel was compared to both R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin) and R-GIFOX (rituximab, gemcitabine, ifosfamide, oxaliplatin). This was presented as a blended comparator, assuming a 50:50 split between the proportions of patients receiving each. Based on clinical opinion obtained by the Review Group, these comparators are considered reasonable. In the absence of clinical data to directly inform the efficacy of R-GDP and R-GIFOX, two alternative data sources were presented as proxy data for the efficacy of these therapies. The Review Group acknowledge the paucity of data available. However, the lack of direct efficacy data means that all relative efficacy and cost-effectiveness outputs must be interpreted with caution.

1. Comparative effectiveness of tisagenlecleucel

The efficacy of tisagenlecleucel in adult patients with relapsed or refractory DLBCL who had received two or more lines of systemic therapy was assessed in two studies: JULIET and Schuster et al. (2017).

JULIET is a phase II, single-arm, global, multi-centre study evaluating the safety and efficacy of tisagenlecleucel in patients with relapsed/refractory DLBCL. As of the 21 May 2018 data cut, 115 patients received infusion with tisagenlecleucel. The median follow-up was 19.3 months (range: not reported). The overall response rate was 54% (95% CI 43% to 64%); 40% had a complete response and 13% had a partial response. The median overall survival was 11.1 months (95% CI 6.6, not reached). The probability of being relapse-free was 64% (95% CI 48% to 76%) at 12 months. The Review Group highlight that these results are likely to be confounded by the high proportion of patients who received bridging chemotherapy prior to tisagenlecleucel infusion. Based on an earlier data cut (December 2017) presented in the EMA Public Assessment Report, an overall response rate of 20.6% (95% CI 13.2% to 29.7%) was observed in patients who received bridging chemotherapy (n=101). This indicates that a proportion of patients were responding to bridging chemotherapy when they received tisagenlecleucel. Due to the extended period between trial enrolment and infusion with tisagenlecleucel, the results may have been enriched with those who had a better prognosis at baseline. The EMA commented in their assessment that baseline characteristics were worse in the group of patients that did not proceed to infusion. In addition, the data are subject to short duration of follow-up and high degree of censoring. This limits any conclusions that may be drawn from the evidence.

Schuster et al. (2017) is a case-series study including 14 patients with DLBCL treated with tisagenlecleucel at a single-site in the United States. Median follow-up, as of the 07 May 2017 data cut, was 28.6 months (range: 3.5 to 37.9). The overall response rate was 50% (95% CI 23% to 77%). Median overall survival was 22.2 months (95% CI not reported) and median progression-free survival was 3.2 months (95% CI 0.9, not estimable). The Review Group highlight that a number of differences exist between the JULIET and Schuster et al. studies, particularly in terms of study design.

In In the absence of direct comparative evidence, matching-adjusted indirect comparisons (MAICs) were conducted using two alternative data sources. In the Applicant base case, data from the pooled JULIET and Schuster et al. studies were compared to the SCHOLAR-1 study. SCHOLAR-1 is an international, multicohort, retrospective study, evaluating overall survival in patients with refractory DLBCL (n=636). SCHOLAR-1 pooled data from the observational follow up of two phase III clinical trials (Lymphoma Academic Research Organization-CORAL and Canadian Cancer Trials Group LY.12) and two observational cohorts (MD Anderson Cancer Centre (MDACC) and University of Iowa/Mayo Clinic (IA/MC) Lymphoma Specialized 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 those received in Ireland. Only overall survival data were available from SCHOLAR-1; progression-free survival was not recorded. Results of the MAIC indicated that tisagenlecleucel was associated with a reduced risk of death when compared to SCHOLAR-1. However, the Review Group had concerns that not all differences between the trials could be accounted for. Of note, patients in the JULIET trial received more prior regimens than those in SCHOLAR-1. In addition, there was a large amount of missing data in SCHOLAR-1. Thus, results should be interpreted with caution.

The Applicant also presented a scenario comparing the pooled tisagenlecleucel studies to the CORAL extension studies. The CORAL extension studies are based on a primary study investigating the efficacy of R-ICE (rituximab, ifosfamide, carboplatin, etoposide) versus R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin), both followed by planned protocol autologous stem cell transplant in patients with relapsed DLBCL (n=477). The extension studies comprised of pooled data from 203 patients who did not proceed to stem cell transplant due to treatment failure and 75 patients whose disease relapsed after receiving stem cell transplant. Patients in these studies received a range of therapies, which are used, in this submission, as proxies for R-GDP and R-GIFOX. Only overall survival data were available from CORAL; progression-free survival was not recorded. Results of the MAIC indicated that tisagenlecleucel was associated with a reduced risk of death when compared to the CORAL extension studies. A number of important variables, such as number of prior

therapies and refractory status, could not be adjusted for. As such, results should be interpreted with caution.

2. Safety of tisagenlecleucel

All patients infused with tisagenlecleucel were included in the safety analysis of JULIET.

Adverse events were experienced by 100% of patients in JULIET. The most common adverse event was cytokine release syndrome (57%), with 23% of the total infused population experiencing cytokine release syndrome of Grade 3-4 severity. Other frequently reported adverse events included anaemia (47%), white blood cell count decreased (36%), neutrophil count decreased (35%) and pyrexia (35%).

The EMA Public Assessment Report has highlighted the risk of serious and life-threatening adverse events in patients treated with tisagenlecleucel. 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 for the management of cytokine release syndrome. All health care professionals who are expected to prescribe, dispense, and administer tisagenlecleucel should undergo adequate training to facilitate identification and management of cytokine release syndrome and serious neurological adverse reactions.

3. Cost effectiveness of tisagenlecleucel

For the cost-effectiveness analysis, the key effectiveness inputs were overall survival and progression-free survival. Cost effectiveness was investigated using a decision tree followed by a partitioned survival model. The decision tree was employed to the tisagenlecleucel arm only to capture the costs and outcomes of patients who do not proceed to infusion. A time horizon of 46 years and a cycle length of one month were employed. The partitioned survival model simulates patients through three health states: progression-free survival, progressed disease and death. All patients infused with tisagenlecleucel start in the progression-free survival state; transitions to the death state could occur from either the progression-free or progressed disease states.

Costs and health-related utilities were allocated to each health state and multiplied by the time spent in that state to calculate the weighted costs and QALYs per cycle. Utility values were derived from the JULIET trial. A once-off utility decrement for adverse events was applied at the start of the first cycle. 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 terminal care costs. The Review Group updated a number of costs to reflect Irish-specific sources. Tisagenlecleucel-specific costs included: leukapheresis, cryopreservation, lymphodepleting and bridging chemotherapy, treatment of cytokine release syndrome, and treatment of B-cell aplasia. The cost of treating cytokine release syndrome comprised intensive care unit admission and treatment with tocilizumab.

Survival outcomes from the pooled JULIET and Schuster et al. (2017) studies were extrapolated, to the full time-horizon of the model, using a variety of extrapolation methods. The Applicant base case employed the hazard ratio derived from the MAIC until year five, followed by parametric extrapolation bounded by the age- and gender-specific natural mortality of the general population. The Review Group considered the Applicant's extrapolation approach to be generally appropriate. However, the Review Group had concerns that the duration of benefit is driven by highly uncertain extrapolation of survival estimates. In addition, the analysis is based on small numbers of patients at risk at the end of follow-up. These factors make it difficult to determine how survival data will develop over longer time horizons. The Review Group did not consider it reasonable to assume that patients would switch to the general population mortality at five years, and so applied a standardised mortality ratio from year five onwards. This was employed to reflect the increased risk of mortality associated with disease-associated comorbidities and treatment-related toxicity.

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 implemented a number of changes to the applicant base case to reflect the most

plausible assumptions. The most significant of these include: the application of a DLBCL-specific standardised mortality ratio to patients alive at five years, using only the JULIET trial data, reducing the number of cycles of R-GDP/R-GIFOX received from six to three, reducing the rate of subsequent stem cell transplant in the comparator arm to reflect Irish clinical practice. Based on these assumptions, tisagenlecleucel was associated with an ICER of €197,119 per QALY (incremental costs €191,050; incremental QALYs 0.97) versus SCHOLAR-1 (base case) and €122,266 per QALY (incremental costs €198,847; incremental QALYs 1.63) versus CORAL extension studies (scenario). The probability of cost-effectiveness at a willingness-to-pay threshold of €45,000 per QALY was 0.1% and 0.5% versus SCHOLAR-1 and CORAL, respectively.

The Applicant's preferred assumptions generated an ICER of €137,988 per QALY (incremental costs €161,126; incremental QALYs 1.16) versus SCHOLAR-1 (base case) and €116,845 per QALY (incremental costs €184,128; incremental QALYs 1.57) versus CORAL extension studies (scenario). The probability of cost-effectiveness at a willingness-to-pay threshold of €45,000 per QALY was 1.4% and 0.7% versus SCHOLAR-1 and CORAL, respectively.

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 the tisagenlecleucel studies), increased the NCPE preferred ICER to €1,035,700 per QALY (incremental costs €224,190; incremental QALYs 0.22) versus SCHOLAR-1 and €734,534 per QALY (incremental costs €220,685; incremental QALYs 0.30) versus the CORAL extension studies. Although the Review Group acknowledge that this is a conservative assumption, it demonstrates the reliance of the model on extrapolation of long-term outcomes.

4. Budget impact of tisagenlecleucel

Tisagenlecleucel is submitted for reimbursement under the Oncology Drugs Management System. The proposed price to wholesaler per infusion is €319,325. The total cost to the HSE inclusive of rebate is €301,762 per infusion; VAT is not applicable. It is anticipated that 12

patients will be treated per annum. This results in a projected five-year gross budget impact of €18.1 million, accounting only for acquisition costs. Taking procedure costs (leukapheresis, lab management, bridging and lymphodepleting chemotherapy) into account, the five-year gross budget impact increases to €18.5 million. Assuming that 12 patients are treated in year 1 and an additional two patients are treated each year, generates a cumulative five-year gross budget impact of €24.1 million and €24.7 million (including procedure costs). This is based on the assumption that increased experience in the administration of tisagenlecleucel 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 tisagenlecleucel (accounting for drug acquisition and procedure costs) is estimated to be between €18.2 and €24.2 million, 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 €20.5 million and €30.2 million.

The Review Group raised concerns that increasing experience with administration of CAR T-cells may lead to greater numbers of patients being treated and therefore, a greater budget impact.

5. Patient submissions

No patient organisation submissions were received during this assessment.

6. Conclusion

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

Following assessment of the applicant's submission, the NCPE recommends that tisagenlecleucel (Kymriah®) for the treatment of adult patients with relapsed or refractory diffuse 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.