Cost-effectiveness of tisagenlecleucel (Kymriah®) for the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse

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 **August 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 paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse. Final data submitted by the applicant was received in August 2019.

Tisagenlecleucel is a chimeric antigen receptor (CAR) T-cell 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.

In the submission, tisagenlecleucel was compared to both blinatumomab and FLA-IDA (fludarabine, cytarabine, idarubicin). The NCPE considered blinatumomab to be the main comparator of interest.

1. Comparative effectiveness of tisagenlecleucel

The efficacy of tisagenlecleucel in patients with paediatric and young adult ALL was assessed in three studies: ELIANA, ENSIGN and B2101J. The data presented below are based on published analyses and were not used in the economic modelling; more recent data cuts were used to inform the economic model.

ELIANA is a phase II, single-arm, global, multi-centre study evaluating the safety and efficacy of tisagenlecleucel. As of the April 2017 data cut, 92 patients (3-25 years) were enrolled and 75 patients had received an infusion with tisagenlecleucel. The results are presented for the infused population. The median follow-up was 13.1 months. The overall response rate,

within three months of tisagenlecleucel administration, was 81% and all patients who had a response to treatment were found to be minimal residual disease negative (<0.01%). The rate of overall survival was 76% (95% CI 63% to 86%) at 12 months; median overall survival was not reached. The rate of event-free survival was 50% (95% CI 35% to 64%) at 12 months; median event-free survival was not reached.

ENSIGN had a similar trial design to that of ELIANA; however, it was only conducted in the US. As of the October 2017 data cut, 73 patients (3-25 years) were enrolled and 58 patients had received infusion with tisagenlecleucel. The results are presented for the infused population. Median follow-up was 19.6 months. The overall response rate was 69% (95% CI 53% to 82%) among the 42 patients who had at least six months of follow-up. The overall survival rate was 63% (95% CI 46% to 76%) at 12 months. Median overall survival was 23.8 months (95% CI 9 months, N.E.).

B2101J is a US-based, single-arm, phase I/II study to determine the safety, tolerability and engraftment potential of tisagenlecleucel in patients with relapsed or refractory B-cell ALL. B2101J was a dose-escalation study and as such, the protocol differed slightly from ELIANA and ENSIGN. Among the 59 patients (1-24 years) who received infusion, overall response rate was 93% (95% CI not reported) and the overall survival rate at 12 months was 79% (95% CI 69% to 91%).

In the absence of direct comparative evidence, a naïve comparison was conducted using data from von Stackelberg *et al*. (2016) to inform the blinatumomab arm and Jeha *et al*. (2006) to inform the FLA-IDA arm. The NCPE review group highlight that any conclusions derived from the naïve comparison should be interpreted with caution due to the unadjusted nature of the data.

2. Safety of tisagenlecleucel

Safety and tolerability was evaluated as a secondary outcome in both ELIANA and ENSIGN, and as part of the primary outcome in B2101J.

Adverse events were observed in 100% of patients in ELIANA. The most common adverse reaction observed in patients were cytokine release syndrome (77%), infections (65%), hypogammaglobulinaemia (47%), pyrexia (40%) and decreased appetite (39%). Grade 3 and 4 adverse events were reported in 88% of patients. The most common of these was cytokine release syndrome (47%).

3. Cost effectiveness of tisagenlecleucel

For the cost-effectiveness analysis, the key effectiveness inputs were overall survival and event-free survival. Cost-effectiveness was investigated using a partitioned survival model with an 88 year time horizon and cycle length of one month. The model simulates patients through three health states: event-free survival, progressed disease and death. All health states are mutually exclusive, and death is an absorbing state. All patients start in the event-free survival state; transitions to the death state could occur from either the event-free or progressed disease states.

Costs and health-related utilities were allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle. Utility values were derived from the ELIANA 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 costs, 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.

Survival outcomes from the pooled ELIANA, ENSIGN and B2101J studies were extrapolated to the full time-horizon of the model, using a variety of extrapolation methods.

Analyses presented in this summary document are based on the list prices of the interventions. The NCPE implemented a number of changes to the applicant base case to reflect the most plausible assumptions. Based on these assumptions and varying the rate of subsequent stem cell transplant between 25% and 82%, tisagenlecleucel was associated with an ICER of between €75,748 per QALY (incremental costs €321,755; incremental QALYs 4.25) and €116,506 per QALY (incremental costs €457,033; incremental QALYs 3.92) versus

blinatumomab. Tisagenlecleucel was associated with an ICER of between €75,990 per QALY (incremental costs €414,637; incremental QALYs 5.46) and €107,163 per QALY (incremental costs €549,914; incremental QALYs 5.13) versus FLA-IDA. Based on the higher ICER estimates, the probability of cost-effectiveness at a threshold of €20,000 per QALY was 0% versus both comparators. This remained at 0% at a threshold of €45,000 per QALY versus FLA-IDA and increased to 2% versus blinatumomab. Varying the proportion of patients alive at five years had the most significant impact on the ICER. Decreasing the proportion of patients alive in the tisagenlecleucel arm at five years from 46% (base case) to 26% generated an ICER of €267,409 per QALY (incremental costs €457,286; incremental QALYs 1.71) versus blinatumomab and €188,490 per QALY (incremental costs €550,167; incremental QALYs 2.92) versus FLA-IDA. The review group highlight that this is a conservative assumption.

Based on the applicant preferred assumptions, tisagenlecleucel was associated with an ICER of €40,643 per QALY (incremental costs €210,392; incremental QALYs 5.18) versus blinatumomab and €51,567 per QALY (incremental costs €342,556; incremental QALYs 6.64) versus FLA-IDA. The probability of cost-effectiveness at a threshold of €20,000 per QALY was 10% versus blinatumomab and 0% versus FLA-IDA. At a threshold of €45,000 per QALY, the probability of cost-effectiveness was 54% versus blinatumomab and 31% versus FLA-IDA.

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; VAT is not applicable. Based on the applicant's estimate of eligible population and assuming a market share of 80% - 90%, a total of 19 patients are expected to be treated with tisagenlecleucel in the first five years. This results in a projected five-year gross budget impact of €5.5 million, accounting only for drug acquisition costs. Taking procedure costs (leukapheresis, lab management, bridging and lymphodepleting chemotherapy) into account, the five-year gross budget impact increases to €5.6 million.

The cumulative five-year net budget impact of tisagenlecleucel (accounting for drug acquisition costs and all tisagenlecleucel procedure costs) is estimated to be €5.6 million.

When additional costs (eg adverse event costs) and cost-offsets are accounted for, the five-year net budget impact is €6.5 million.

5. Patient submissions

No patient organisation submissions were received during this HTA.

6. Conclusion

Following assessment of the applicant's submission, the NCPE recommends that tisagenlecleucel (Kymriah®) for the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse 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.*