NCPE Assessment

Technical Summary

Ciltacabtagene autoleucel (cilta-cel)

Carvykti®

HTA ID: 22021

27 September 2023

Applicant: Janssen Sciences Ireland

Ciltacabtagene autoleucel for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost effectiveness of ciltacabtagene autoleucel (Carvykti®) for this indication.

Following assessment of the Applicant's submission, the NCPE recommends that ciltacabtagene autoleucel (Carvykti®) not be considered for reimbursement 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 (Janssen Sciences Ireland) Health Technology Assessment of ciltacabtagene autoleucel (Carvykti®). 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 November 2022, Janssen Sciences Ireland submitted a dossier, which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of ciltacabtagene autoleucel (Carvykti®), herein referred to as 'cilta-cel'. Cilta-cel is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM), who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 monoclonal antibody and have demonstrated disease progression on the last therapy. Janssen Sciences Ireland is seeking reimbursement of cilta-cel on the Oncology Drugs Management System. Cilta-cel is a BCMA-targeted 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: apheresis, bridging therapy, and conditioning therapy. Post-infusion monitoring should occur daily for the first 14 days after infusion, in a qualified treatment centre. Patients should remain within proximity of the qualified treatment centre for up to four weeks post-infusion. Cilta-cel is the first CAR T-cell therapy for RRMM to be assessed by the NCPE.

The Applicant anticipates that cilta-cel will be used in line with its licensed indication (as stated above). The treatment pathway at this line of therapy is highly heterogeneous. There is no universal standard-of-care. For the comparator arm in this analysis, the Applicant defined a 'physician's choice' comparator, which comprised six commonly used regimens in this setting. These regimens were carfilzomib and dexamethasone; ixazomib, lenalidomide and dexamethasone; daratumumab, bortezomib and dexamethasone; carfilzomib, lenalidomide and dexamethasone; pomalidomide and dexamethasone; pomalidomide, bortezomib and dexamethasone.

1. Comparative effectiveness of ciltacabtagene autoleucel

CARTITUDE-1 trial

The efficacy and safety of cilta-cel was investigated in the CARTITUDE-1 trial. This was a phase Ib/II, open-label, single-arm study, which enrolled 113 patients with RRMM who received at least three prior regimens. Prior treatment with a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody was required (i.e. triple-class exposed). The intention-to-treat (ITT) population was defined as patients who

underwent apheresis (n=113), while the modified ITT (mITT) population was defined as patients who received infusion with cilta-cel (n=97). Cilta-cel was administered as a single intravenous infusion at total targeted dose of $0.75x10^6$ CAR-positive viable T-cells per kilogram of body weight. Bridging therapy and conditioning therapy were permitted prior to cilta-cel infusion.

The data presented are based on the final data cut of CARTITUDE-1 (data cut-off: 11 January 2022; median follow-up: 27.7 months). The primary endpoint, overall response rate, was 84.1% (95% CI 76.0 to 90.3) in the ITT population and 97.9% (95% CI 92.7 to 99.7) in the mITT population. Progression-free survival (PFS) and overall survival (OS) were secondary endpoints. PFS data were immature; 47.8% of patients in the ITT population and 44.3% in the mITT population experienced a PFS event. Median PFS was 28.02 months (95% CI 20.11 to not estimable) in the ITT population and not reached in the mITT population. OS data were also immature; 34.5% in the ITT population and 30.9% in the mITT population experienced an OS event. Median OS was not reached in either population.

The Review Group had concerns regarding the immaturity of the PFS and OS data, which results in a high degree of uncertainty in long-term survival predictions. It is unclear if the benefit in overall response rate will translate to a long-term survival benefit. Additionally, due to the single-arm nature of the trial, it is not possible to contextualise the efficacy results or directly ascertain the treatment effect of cilta-cel compared to standard-of-care in Ireland.

Indirect treatment comparison

Due to the lack of direct comparative evidence, an indirect treatment comparison was conducted to generate estimates of relative effectiveness. The LocoMMotion study was used to inform efficacy of the physician's choice arm. LocoMMotion is a non-interventional, multinational, real-world study of standard-of-care therapies used in patients (n=248) with triple-class exposed RRMM. This study was designed a priori to serve as an external control cohort for CARTITUDE-1. The eligibility criteria and assessed outcomes were aligned with those of CARTITUDE-1. Of note, a total of 92 different treatment regimens were identified as standard-of-care therapies in the LocoMMotion study. To derive estimates of relative

effectiveness, propensity score weighting was used in an attempt to adjust for known confounders. Both unadjusted and adjusted results indicated that cilta-cel is associated with significantly improved PFS and OS versus physician's choice therapies. Sensitivity analysis indicated that the base case results were robust to alternative assumptions, supporting the Applicant's findings. Results of a scenario, which included efficacy data of only the treatment regimens (n=6) defined in the physician's choice comparator arm, were aligned with the base case (which used all regimens in the LocoMMotion study, n=92). There is sizable inherent uncertainty in the comparative evidence relative to the treatments in LocoMMotion, due to the single-arm nature of CARTITUDE-1. However, the Applicant performed patient reweighting using an extensive number of patient characteristics, and provided scenario analyses as requested by the Review Group. Overall, the Review Group were satisfied that the limited data were utilised appropriately.

2. Safety of ciltacabtagene autoleucel

The safety profile of cilta-cel in the CARTITUDE-1 trial was consistent with the established safety profile of other CAR T-cell therapies. No new safety signals were identified. A number of risk minimisation measures are outlined in the summary of product characteristics.

3. Cost effectiveness of ciltacabtagene autoleucel

Methods

A de novo partitioned survival model was used to evaluate the cost effectiveness of cilta-cel. A decision tree was used to capture the costs and outcomes associated with the pre-treatment phase (apheresis, bridging therapy, conditioning therapy) of cilta-cel. From the decision tree, patients in the cilta-cel arm entered the partitioned survival model and either received treatment with cilta-cel or no treatment. OS and PFS of these cohorts were modelled separately, and subsequently combined to represent the full CARTITUDE-1 population. Patients in the physician's choice arm entered the partitioned survival model directly. The partitioned survival model included three mutually exclusive health states; progression-free, post-progression and death. The key efficacy inputs, OS and PFS, were modelled using treatment group-specific parametric distributions fitted to time-to-event data from CARTITUDE-1 (cilta-cel) and LocoMMotion (physician's choice). The LocoMMotion data were reweighted such that the distribution of baseline characteristics was similar to

CARTITUDE-1.

Progression-free utility data were derived from the CARTITUDE-1 trial. The low number of responses in the CARITUDE-1 trial is a considerable limitation of the utility data and limits the robustness of the data generated. Progressed disease utility data were sourced from the NICE HTA appraisal of isatuximab in combination with pomalidomide and dexamethasone (NICE TA658). The model included drug acquisition, administration, monitoring, subsequent treatment, and adverse event costs.

The Review Group identified a number of limitations in the Applicant's base case, which were explored in the NCPE-adjusted base case. The most notable of these included: employing a Weibull model to extrapolate the PFS data of CARTITUDE-1 (instead of a log-normal), and employing a log-logistic model to extrapolate the OS data of CARTITUDE-1 and LocoMMotion (instead of a log-normal and exponential, respectively).

Results

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

Table 1 Applicant's base case incremental cost-effectiveness results

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER[a] (€/QALY)
Physician's Choice[b]	100,476	1.03	-	-	-
Cilta-Cel	386,005	3.98	285,529	2.95	96,892

Cilta-cel: Ciltacabtagene autoleucel; **ICER:** Incremental cost-effectiveness ratio; **QALY:** Quality-adjusted life year.
[a]Corresponding probabilistic ICER using 1,000 iterations =€98,419 per QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Total costs and QALYS presented are discounted (4%).
[b]A commercial-in-confidence patient access scheme (CIC PAS) is in place for carfilzomib, daratumumab, ixazomib and pomalidomide. CIC PAS not included in this table.

Table 2 NCPE-adjusted base case incremental cost-effectiveness results

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER[a] (€/QALY)
Physician's Choice[b]	101,792	1.12	-	-	-
Cilta-Cel	390,668	3.47	288,876	2.35	122,926

Cilta-cel: Ciltacabtagene autoleucel; **ICER:** Incremental cost-effectiveness ratio; **QALY:** Quality-adjusted life year.
[a] Corresponding probabilistic ICER using 1,000 iterations =€122,574 per QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Total costs and QALYS presented are discounted (4%).
[b] A commercial-in-confidence patient access scheme (CIC PAS) is in place for carfilzomib, daratumumab, ixazomib and pomalidomide. CIC PAS not included in this table.

Sensitivity analysis

The probabilities of cost effectiveness, for cilta-cel versus physician's choice, under the NCPE-adjusted base case assumptions were 0% at the €20,000 per QALY and 0% at the €45,000 per QALY thresholds. Deterministic one-way sensitivity analysis indicated that the most influential parameters in the model, for both the Applicant and the NCPE-adjusted base case, related to OS curve parameters of the CARTITUDE-1 data.

A price-ICER analysis, conducted using the NCPE-adjusted base case, indicated that a 59.1% and 75.3% reduction in the price-to-wholesaler of cilta-cel was required to meet the €20,000 per QALY and €45,000 per QALY thresholds, respectively. Commercial-in-confidence patient access scheme discounts are in place for comparator regimens. When these were accounted for, a higher price reduction on cilta-cel was required to reach these thresholds.

4. Budget impact of ciltacabtagene autoleucel

The proposed price-to-wholesaler per single-dose intravenous infusion of cilta-cel is €420,000. The total cost to the HSE, inclusive of rebate and VAT, is €481,950 (€385,350 excluding VAT).

The eligible population is defined as patients with triple-class exposed RRMM who are eligible for treatment in the fourth-line setting. In line with the CARTITUDE-1 trial, the Applicant assumed that 86% of patients considered for treatment with cilta-cel will receive cilta-cel. This is due to factors such as manufacturing failure, adverse events, and death prior to infusion, which prevent patients proceeding to infusion. Given current capacity and a relatively low estimated market share, it was estimated that 10 patients will receive treatment in year one, increasing to 15 from year five onwards. The five-year cumulative treated population was estimated to be 72 patients. Based on these population estimates, the five-year cumulative gross drug budget impact was estimated to be €34.8 million (€27.8 million excluding VAT). The five-year cumulative net drug budget impact was €30.3 million (€23.9 million excluding VAT). Cilta-cel is associated with a number of pre-treatment costs, including bridging therapy and conditioning therapy. These were not considered in the estimates presented here. Their inclusion would increase the gross and net drug budget impact estimates.

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. The Review Group highlight that the number of patients treated with cilta-cel is contingent on capacity within the health service to provide such treatment. Currently, treatment of adult patients is limited to one accredited treatment centre in Ireland. Should more centres become accredited, or should capacity increase within the current centre, more patients are likely to receive treatment. In this instance, the gross and net drug budget impacts are likely to increase considerably.

5. Patient Organisation Submission

A patient organisation submission was received from Multiple Myeloma Ireland (MMI).

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that cilta-cel 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.*