NCPE Assessment

Technical Summary

Ciltacabtagene autoleucel (Carvykti®)

HTA ID: 2402

16 December 2025

Applicant: Johnson and Johnson Innovative Medicine

Ciltacabtagene autoleucel for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least one prior therapy, including an immunomodulatory agent and a proteasome inhibitor, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide.

NCPE
National Centre for Pharmacoeconomics, Ireland

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

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 (Johnson and Johnson Innovative Medicine) 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 February 2025, Johnson and Johnson Innovative Medicine submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of ciltacabtagene autoleucel (Carvykti®) for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM), who have received at least one prior therapy, including an immunomodulatory agent (IMiD) and a proteasome inhibitor (PI), have demonstrated disease progression on the last therapy, and are refractory to lenalidomide. Johnson and Johnson Innovative Medicine is seeking reimbursement of ciltacabtagene autoleucel, hereafter referred to as cilta-cel, on the Oncology Drugs Management System.

Cilta-cel is a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T-cell (CAR-T) therapy. It is a genetically modified autologous cell-based product. Cilta-cel is administered as a once-off, single-dose intravenous infusion. Prior to infusion, a patient must undergo apheresis and lymphodepletion; they may also receive bridging therapy.

Cilta-cel was approved for HSE reimbursement, in October 2025, for a different indication. It was approved for the treatment of adult patients with RRMM, who have received at least three prior therapies, including an IMiD, a PI and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

The treatment pathway for RRMM is highly heterogeneous. There is no universal standard-of-care. The Applicant identified the following drug regimens as relevant comparators to cilta-cel: carfilzomib in combination with dexamethasone (car+dex), daratumumab in combination with bortezomib and dexamethasone (dar+bor+dex), pomalidomide in combination with bortezomib and dexamethasone (pom+bor+dex) and pomalidomide in combination with dexamethasone (pom+dex). Teclistamab monotherapy was not included as a comparator, which the Review Group considered to be a limitation of the assessment.

1. Comparative effectiveness of cilta-cel

The clinical efficacy of cilta-cel, for this indication, was informed by outcomes from the phase III, randomised, open-label, CARTITUDE-4 trial. Eligible participants were adults with RRMM resistant to lenalidomide, who had received one to three prior lines of therapy including an IMiD and a PI, and who experienced disease progression on the last treatment.

Participants (n=419) were randomly assigned to receive either cilta-cel (n=208) or the control comparator (n=211), which was Physician's treatment of choice from either pom+bor+dex or daratumumab in combination with pomalidomide and dexamethasone (dar+pom+dex). The primary efficacy endpoint was progression-free survival (PFS). Key secondary endpoints were complete response, overall response, minimal residual disease negativity, and overall survival (OS). Outcomes on health-related quality of life (HRQoL) were also collected. The most recent data cut was May 2024; median follow-up was 33.6 months.

Across all endpoints, outcomes were more favourable in the cilta-cel arm compared to the control arm. Median PFS was not sufficiently mature to be estimable in the cilta-cel arm (95% CI, 34.4 months to NE months). Median PFS in the control arm was 11.8 months (95% CI, 9.7 months to 14.0 months). Overall response and complete response rates were 84.6% (95% CI, 79.0% to 89.2%) and 76.9% (95% CI, 70.6% to 82.5%) respectively in the cilta-cel arm, compared to 67.3% (95% CI, 60.5% to 73.6%) and 24.2% (95% CI, 18.6% to 30.5%) respectively in the control arm. Minimal residual disease negativity was 62.0% (95% CI, 55.0% to 68.6%) in the cilta-cel arm and 18.5% (95% CI, 13.5% to 24.4%) in the control arm. OS data was immature at the May 2024 data cut. Limitations of the clinical evidence included crossing of the two Kaplan-Meier curves for PFS at three months after randomisation, with 31 and 27 PFS events having occurred in the cilta-cel and control arms, respectively. The cause of this imbalance remains unclear. Furthermore, the control arm included the regimen dar+pom+dex as a comparator. This is not reimbursed by the HSE and, therefore, was not a relevant comparator in this assessment. Finally, the open-label design of CARTITUDE-4 may have influenced patient-reported outcomes, including HRQoL and adverse events (AEs), due to awareness of treatment allocation.

Outcomes from CARTITUDE-4 informed comparative efficacy of cilta-cel versus pom+bor+dex. In the absence of direct comparative evidence for cilta-cel versus the other comparators, unanchored indirect treatment comparisons (ITCs) were performed. Clinical efficacy of car+dex, dar+bor+dex and pom+dex were informed by data from the CASTOR, CANDOR and APOLLO trials, respectively. To control for confounding, the matching-adjusted indirect comparison (MAIC) method was used in which individual participant data from CARTITUDE-4 were reweighted using propensity-score methods, in order to align with comparator trial populations in terms of a number of prognostic and/or effect-modifying variables. Relative treatment effects for OS and PFS were estimated as hazard ratios. Results

from the ITCs suggested that cilta-cel was associated with increases in OS and PFS compared with all comparators. Unanchored ITCs are associated with a substantially higher risk of bias and corresponding lower certainty of evidence than randomised controlled trials. In particular, validity of the unanchored MAIC approach relies on the assumption that all prognostic and effect-modifying variables have been adjusted for. While the Applicant adjusted for a number of relevant variables, others could not be included (e.g., cytogenetic risk), leading to a risk of confounding bias. Other limitations noted by the Review Group included the low effective sample sizes and the immaturity of the data (particularly for OS), leading to uncertainty in the long-term treatment effectiveness.

2. Safety of cilta-cel

The clinical safety of cilta-cel was informed by data from the CARTITUDE-4 trial. Participants who were randomised and who received any part of study treatment were included in the safety analysis set (n=416). All participants in CARTITUDE-4 experienced at least one AE. Neutropenia and thrombocytopenia were frequently reported AEs in both the cilta-cel and control arms (89.9% and 85.6% respectively for neutropenia; 54.3% and 32.2% respectively for thrombocytopenia). AEs specifically attributed to cilta-cel were reported in 82.2% of participants assigned to the cilta-cel arm. These included cytokine release syndrome and CAR-T associated neurotoxicity. Cilta-cel must be administered in a qualified treatment centre with access to the requisite emergency equipment and medication pre- and post-infusion. 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.

3. Cost effectiveness of cilta-cel

Methods

Cost-effectiveness was assessed, from the perspective of the HSE, using a partitioned survival model developed in Microsoft Excel®. The population considered was adult patients with lenalidomide-refractory RRMM, who had previously received between one and three lines of therapy, and whose disease progressed on the last treatment. Cilta-cel was the modelled intervention. The modelled comparators were car+dex, dar+bor+dex, pom+bor+dex, and pom+dex.

The cost effectiveness model (CEM) comprised three mutually exclusive health states: progression Free [PF], Progressed Disease [PD] and Death. All patients entered the model in the PF health state and were assigned to treatment with either cilta-cel or one of the modelled comparators. During each model cycle, patients could either remain in their current state, transition to the PD state, or transition from the PF or PD states to the Death state. Transitions to improved health states were not permitted. Model cycle length was one week. A lifetime horizon of 40 years was assumed. A half-cycle correction was applied.

In the Applicant base case, it was assumed that 30% of patients treated with cilta-cel would be cured from Year Five onwards. This assumption was informed by recently published, follow-up data from the CARTITUDE-1 trial. CARTITUDE-1 was a phase Ib/II, single-arm study of cilta-cel in adults with RRMM with triple class exposed disease (previous treatments included a PI, an IMiD and an anti-CD38 antibody). The populations recruited to the CARTITUDE-4 and CARTITUDE-1 trials were different. Median follow-up for CARTITUDE-1 was 61.3 months. The Kaplan Meier data indicated that, at 60 months, only 16 out of 97 patients had not yet progressed or died; some progression events occurred between four and five years of follow-up. The Review Group considered the assumption of cure to be highly uncertain.

PFS and OS were modelled independently. Outcomes from CARTITUDE-4 were used to inform treatment effectiveness for cilta-cel versus pom+bor+dex; outcomes from the ITC were used to inform treatment effectiveness for cilta-cel versus all other comparators. OS was constrained by Irish general population mortality; PFS was constrained by the selected OS distribution. Treatment costs were based on time to treatment discontinuation (TTD), which was constrained by PFS.

The Applicant selected an exponential distribution to extrapolate OS for comparators over the lifetime horizon of the CEM. However, the Review Group considered that the gamma distribution generated more plausible extrapolations of OS.

The Applicant selected a log-logistic distribution to extrapolate PFS for cilta-cel over the lifetime horizon of the CEM. The Review Group considered that the gamma distribution generated estimates of PFS for cilta-cel that were more conservative but equally plausible. In the absence of longer-term outcome data, survival estimates remain uncertain.

A systematic literature review was conducted to identify HRQoL data to inform utility values

in the CEM. Data from the CARTITUDE-4 and APOLLO trials were used to inform utility values for the PF and PD health states, respectively. Maturity of post-progression data from CARTITUDE-4 was considered insufficient to inform the PD health state. Data collected using the EQ-5D-5L instrument was converted to EQ-5D-3L using the van Hout algorithm. In the CEM, utility values were extrapolated for the remainder of the time horizon based on utility observed at 24 months and 18 months for cilta-cel and the comparators, respectively. The Review Group considered this approach to lack rationale and increase uncertainty. Extrapolation from the same time point for both cilta-cel and comparators is a more consistent approach.

Costs and resources included were drug costs, drug administration costs, subsequent treatment costs, AE costs and disease management costs. A once-off, end-of-life cost was also included. The Applicant included a cost for hospitalisation which assumed an in-patient stay of 16.6 days; this was informed by the CARTITUDE-4 trial. Lymphodepletion, cilta-cel administration (at five to seven days following the start of lymphodepletion) and 14-day post-infusion monitoring should take place in a hospital setting.

Results

Results of the Applicant base case deterministic cost-effectiveness analysis are presented in Table 1.

Table 1: Applicant base case incremental cost-effectiveness results (pairwise ICERs) [a, b, c, d,e]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Cilta-cel	550,234	7.32	-	-	-
Car+dex	425,429	2.91	124,805	4.41	28,326
Dar+bor+dex	299,023	2.33	251,211	4.98	50,400
Pom+bor+dex	271,796	2.33	278,438	4.98	55,880
Pom+dex	207,202	2.13	343,032	5.18	66,199

Car+dex: carfilzomib in combination with dexamethasone; **cilta-cel**: ciltacabtagene autoleucel; **dar+bor+dex:** daratumumab in combination with bortezomib and dexamethasone; **ICER**: incremental cost-effectiveness ratio; **pom+bor+dex**: pomalidomide in combination with bortezomib and dexamethasone; **pom+dex:** pomalidomide in combination with dexamethasone; **QALY**: quality-adjusted life year

[a] Corresponding probabilistic ICERs using 1,000 iterations (€ per QALY): cilta-cel versus car+dex: €25,874; cilta-cel versus dar+bor+dex: €48,637; cilta-cel versus pom+bor+dex: €55,101; cilta-cel versus pom+dex: €65,282. Figures in the table are rounded, and so calculations may not be directly replicable

[b] A commercial in confidence Patient Access Scheme is in place for carfilzomib and daratumumab; not included in this table.

[c] Total costs and QALYs presented are discounted (4%).

[d] Figures in the table are rounded; calculations may not be directly replicable.

[e] The Review Group were informed in the final stages of the NCPE assessment (post Factual Accuracy Check) that there had been a price realignment. Effective 01 October 2025, the price to wholesaler per single-dose of cilta-cel is €393,397.01. However, due to the advanced stage of the NCPE assessment process at which the Review Group were informed of this price realignment, all cost-effectiveness and budget impact analyses presented in this technical summary document are informed by the original, pre-01 October 2025 price to wholesaler for cilta-cel of €420,000. The Review Group did not anticipate that the October 2025 price realignment for cilta-cel would have a major impact on cost-effectiveness results.

Several changes were made to inform the NCPE adjusted base case. These included: removing the assumption of cure; selecting the gamma distribution for extrapolation of OS for the comparators; selecting the gamma distribution for extrapolation of PFS for cilta-cel; assuming a 19-day inpatient stay to inform hospitalisation cost for cilta-cel; and extrapolation of utility values over the time horizon to be based on observed utility at 18 months for both cilta-cel and comparators. Results of the NCPE adjusted base case are presented in Table 2.

Table 2: NCPE adjusted base case incremental cost-effectiveness results [a, b, c, d, e]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Cilta-cel	723,864	7.01	-	-	-
Car+dex	394,763	2.74	329,101	4.27	77,024
Dar+bor+dex	297,731	2.33	426,132	4.68	90,972
Pom+bor+dex	291,690	2.46	432,174	4.55	94,919
Pom+dex	195,399	2.06	528,465	4.95	106,658

Car+dex: carfilzomib in combination with dexamethasone; c**ilta-cel**: ciltacabtagene autoleucel; **dar+bor+dex:** daratumumab in combination with bortezomib and dexamethasone; **ICER**: incremental cost-effectiveness ratio; **pom+dex:** Pomalidomide in combination with dexamethasone; **pom+bor+dex**: pomalidomide in combination with bortezomib and dexamethasone; **QALY**: quality-adjusted life year

[a] Corresponding probabilistic ICERs using 1,000 iterations: cilta-cel versus car+dex: €75,262 per QALY; cilta-cel versus dar+bor+dex: €90,652 per QALY; cilta-cel versus pom+bor+dex: €93,786 per QALY; cilta-cel versus pom+dex: €106,851 per QALY. Figures in the table are rounded, and so calculations may not be directly replicable.

[b] A commercial in confidence Patient Access Scheme is in place for carfilzomib and daratumumab; not included in this table.

[c] Total costs and QALYs presented are discounted (4%).

[d] Figures in the table are rounded; calculations may not be directly replicable.

[e] The Review Group were informed in the final stages of the NCPE assessment (post Factual Accuracy Check) that there had been a price realignment. Effective 01 October 2025, the price to wholesaler per single-dose of cilta-cel is €393,397.01. However, due to the advanced stage of the NCPE assessment process at which the Review Group were informed of this price realignment, all cost-effectiveness and budget impact analyses presented in this technical summary document are informed by the original, pre-01 October 2025 price to wholesaler for cilta-cel of €420,000. The Review Group did not anticipate that the October 2025 price realignment for cilta-cel would have a major impact on cost-effectiveness results.

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 included choice of OS curve for the comparators, and choice of PFS curve for cilta-cel.

Under NCPE adjusted base case assumptions, the probability of cost-effectiveness of cilta-cel versus car+dex, dar+bor+dex, pom+bor+dex, and pom+dex at the €45,000 per quality adjusted life year (QALY) threshold was 10.6%, 1.3%, 4.7% and 0%, respectively. The probability of cost-effectiveness of cilta-cel at the €20,000 per QALY threshold was less than 5% across all comparisons. A price-ICER analysis, using NCPE adjusted base case assumptions, indicated that percentage reductions between 43% and 86% (depending on the comparator) would be required to meet the €45,000 per QALY cost-effectiveness

threshold. Percentage reductions of between 70% and 95% would be required to meet the €20,000 per QALY threshold.

4. Budget impact of cilta-cel

Following a price realignment 01 October 2025, the price to wholesaler per single-dose intravenous infusion of cilta-cel is €393,397. The total cost to the HSE is €448,473 (inclusive of VAT and Framework Agreement rebate). The NCPE were informed of the price realignment in the final stages of the assessment. All cost-effectiveness and budget impact analyses, conducted and presented in this technical summary, were informed by the original price to wholesaler (pre-October 2025; price to wholesaler €420,000).

Eligible patients were adult patients with RRMM who have received at least one prior therapy including a PI and an IMiD, who experience disease progression on the last therapy, and who are refractory to lenalidomide in the second- or third-line setting. Eligible patient numbers were estimated to be 146 in Year One, rising to 154 in Year Five. Eligible patient population estimates and market share values for cilta-cel and comparators were highly uncertain. The Applicant-estimated five-year cumulative gross and net drug-budget impacts for cilta-cel were €34.5 million and €26.2 million, respectively, including VAT. This does not include costs directly related to cilta-cel infusion such as apheresis, bridging therapy, and lymphodepletion.

5. Patient Organisation Submission

A patient organisation submission was received from Multiple Myeloma Ireland.

6. Conclusion

The NCPE recommends that ciltacabtagene autoleucel (Carvykti®) 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.