NCPE Assessment

Technical Summary

Teclistamab (Tecvayli®)

HTA ID:22064

03 July 2024

Applicant: Janssen Sciences Ireland UC

Teclistamab as monotherapy for the treatment of adult patients with relapsed and 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 teclistamab (Tecvayli®). Following assessment of the Applicant's submission, the NCPE recommends that teclistamab (Tecvayli®) 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 UC) Health Technology Assessment of teclistamab (Tecvayli®). 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 May 2023, Janssen Sciences Ireland UC submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of teclistamab (Tecvayli®) as monotherapy for the treatment of adult patients with relapsed, refractory multiple myeloma (RRMM), 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. Janssen Sciences Ireland UC is seeking reimbursement of teclistamab on the Oncology Drugs Management Scheme.

Teclistamab is a bispecific antibody that targets the CD3 receptor expressed on the surface of T cells and B cell maturation antigen (BCMA), which is expressed on the surface of malignant multiple myeloma (MM) B-lineage cells, as well as late-stage B cells and plasma cells. With its dual binding sites, teclistamab is able to draw CD3+ T cells in close proximity to BCMA+ cells, resulting in T cell activation and subsequent lysis and death of BCMA+ cells. The recommended dose is 1.5mg/kg administered via subcutaneous injection once weekly, preceded by step-up doses of 0.06mg/kg once on Day 1 and 0.3 mg/kg once on Day 3 (in week one). Patients who achieve a complete response (CR), or better, for a minimum of six months may switch to 1.5mg/kg once every two weeks as per the summary of product characteristics (SmPC).

The current standard of care (SOC) for the treatment of this patient population in Ireland is difficult to define but consists primarily of triplet chemotherapy regimens. The Applicant included a basket comparator of the six most frequently used regimens in Ireland, henceforth referred to as treatment of physician's choice (TPC). These include daratumumab plus bortezomib plus dexamethasone (Dar+Bor+Dex); carfilzomib plus dexamethasone (Car+Dex); carfilzomib plus lenalidomide plus dexamethasone (Car+Len+Dex); ixazomib plus lenalidomide plus dexamethasone (Ixa+Len+Dex); pomalidomide plus dexamethasone (Pom+Dex); and pomalidomide plus bortezomib plus dexamethasone (Pom+Bor+Dex). The Review Group highlight that this is a rapidly evolving treatment area with a number of new treatments licensed (but not yet reimbursed) for triple-class exposed patients with RRMM including ciltacabtagene autoleucel (cilta cel) (currently under consideration for reimbursement by the HSE; considered a comparator in an additional analysis by the Applicant), idecabtagene autoleucel, belantamab mafodotin, selinexor with dexamethasone,

elranatamab, talquetamab and melphalan flufenamide.

1. Comparative effectiveness of teclistamab

The efficacy and safety of teclistamab was assessed in the MajesTEC-1 trial (n=165). MajesTEC-1 is a single-arm, open label, phase I/II trial of patients with triple class exposed RRMM after at least three prior lines of therapy. Teclistamab was administered at a dose of 1.5mg/kg once weekly (preceded by step-up doses) until disease progression or unacceptable toxicity. The primary endpoint of MajesTEC-1 was objective response rate (ORR) as assessed by an Independent Review Committee, and key secondary endpoints included progression free survival (PFS) and overall survival (OS) [median follow-up 30.4 months]. In total, 63% achieved an ORR (95% confidence interval [CI] 55.2, 70.4). The median OS was 22.2 months (OS data are immature) and median PFS was 11.4 months. Limitations of the MajesTEC-1 trial include the single-arm, open label design, the immature OS data (57% of events have occurred at the most recent data-cut), and generalisability of the trial population (participants included those with good performance status and of relatively young age, limiting the information on tolerability of the treatment in a less fit, older patient population). The small sample size (n=165) adds to the uncertainty. The relevance of ORR to inform clinical benefit evaluations is limited, and robust demonstrations of durable responses are needed to conclude clinical benefit.

The Applicant conducted an indirect treatment comparison (ITC) comparing teclistamab to TPC using observational data from the LocoMMotion study (model option 1) and LocoMMotion plus MoMMent studies (model option 2). A further ITC comparing teclistamab to cilta cel (alternative comparator) was provided using data from the CARTITUDE-1 trial. LocoMMotion was a prospective, non-interventional study of SOC in patients with RRMM who have received at least three prior lines of therapy. MoMMent is an ongoing prospective, observational study identical to LocoMMotion initiated to continue documenting SOC and associated outcomes in patients with RRMM. CARTITUDE-1 was a phase Ib/II, open-label, single-arm study investigating the efficacy of cilta cel in patients with triple class exposed RRMM. The Applicant used the LocoMMotion study (model option 1) in their base case, whilst the NCPE adjusted base case used LocoMMotion plus MoMMent studies (model option 2). The Applicant performed patient re-weighting using an extensive number of patient characteristics, and relevant scenario analyses. In the Applicant's base case (model

option 1) teclistamab was associated with a statistically significant improvement in PFS (hazard ratio [HR] 0.46, 95% CI 0.34, 0.62) and OS (HR 0.61, 95% CI 0.45, 0.83) versus TPC. In the NCPE adjusted base case (model option 2) teclistamab was associated with a statistically significant improvement in PFS (HR 0.49, 95% CI 0.36, 0.65) and OS (HR 0.66, 0.48, 0.89) versus TPC. When compared to cilta cel (additional comparator), teclistamab was associated with a statistically significant increased risk of progression (HR 2.40, 95% CI 1.55, 3.73) or death (HR 2.68, 95% CI 1.48, 4.83).

2. Safety of teclistamab

At least one (any grade) treatment emergent adverse event (TEAE) was reported for all 165 participants in MajesTEC-1 (100%). The most frequently reported TEAEs included cytokine release syndrome (CRS), neutropenia, anaemia, and lymphopenia. The safety profile is consistent with the mechanism of action with respect to T-cell activation and targeting of B cells. The SmPC carries special warnings for CRS, neurologic toxicities, infections, hepatitis B virus reactivation, hypogammaglobulinemia, vaccines (immune response to vaccines may be reduced when taking teclistamab), and neutropenia. The SmPC recommends that treatment should be initiated with teclistamab according to the step-up dosing schedule to reduce risk of CRS, and pre-treatment medicinal products should be administered prior to each step-up dose. Patients should remain within the proximity of a healthcare facility and be monitored daily for 48 hours during step-up dosing.

3. Cost effectiveness of teclistamab

The Applicant has compared the cost-effectiveness of teclistamab to TPC in the base case and to cilta cel in an additional analysis.

Methods

A three health-state partitioned survival model (PSM) was submitted by the Applicant. The treatment effects captured by the model were the delay of disease progression and death. Key efficacy inputs were PFS and OS. The population was based on the MajesTEC-1 trial. Treatment duration for teclistamab was informed by time-to-treatment discontinuation data from MajesTEC-1. OS and PFS were modelled independently. The proportion of patients in each health state over time was derived directly from the OS and PFS area under the curve, using treatment group-specific parametric distributions fitted to time-to-event data. For the Applicant's base case, HRs obtained from the ITC (model option 1) were applied to the

survival functions for OS and PFS associated with teclistamab and TPC. In each cycle, patients accrue quality adjusted life years (QALYs) and incur costs based on the utilities and costs specified for the health-state occupied, the relevant treatment arm, and the time on treatment. The Applicant utilised a landmark approach where the efficacy inputs for teclistamab were stratified by a weighted sum of two subgroups defined according to response status at the eight-week landmark point. Patients were split into categories based on their achieved response at the landmark point: Subgroup 1 (patients with a partial response or better, or stable disease, or with non-evaluable data) and Subgroup 2 (patients with progressed disease or who had died). Given the relatively small sample size (n=165) available for extrapolation, the Review Group did not consider it appropriate to disaggregate the data. Utility values were derived from EQ-5D-5L data collected in MajesTEC-1, mapped to EQ-5D-3L. The Applicant implemented time-dependent utilities, which improved the longer a patient was on treatment and progression free. The Review Group highlighted concerns that the time-dependant utilities used by the Applicant for the pre-progression state may lack face validity at the end of the time period; these are higher than values seen in previous submissions for this population and are higher than the general population utility. Also, the values may be biased due to missing values from frailer patients and given the single-arm, open-label nature of the trial. There were a limited number of post-progression events in the EQ-5D analysis set. A UK appraisal of isatuximab (TA658) for the fourth-line treatment of MM was used as a source for post-progression utilities in the Applicant's base case and NCPE adjusted base case.

The Review Group identified a number of limitations in the Applicant's base case, which were addressed through changes in the NCPE adjusted base case. These changes included: 1) Efficacy data for the ITC: Applicant base case used LocoMMotion data (model option 1); NCPE adjusted base case used LocoMMotion plus MoMMent data (model option 2); 2) Model structure: NCPE adjusted base case removed the Subgroup 1 and Subgroup 2 landmark approach and instead utilised a standard PSM approach; 3) Utilities: Applicant base case used time-dependent treatment utilities in the Progression Free state; NCPE adjusted base case used mean health state utilities; 4) Treatment waning: Applicant base case assumed a lifetime benefit of teclistamab; NCPE adjusted base case incorporated treatment waning starting at five years and increasing up to ten years. Costs and outcomes were discounted at an annual rate of 4%. The HSE perspective was taken.

Results

The results of the Applicant's base case deterministic cost-effectiveness analysis are presented in Table 1 (versus TPC) and Table 2 (versus cilta cel). Respective results of the NCPE adjusted base case are presented in Tables 3 and 4. The probabilities of cost-effectiveness, for teclistamab versus TPC, in the NCPE adjusted base case was 0% at both thresholds of €20,000/QALY and €45,000/QALY. For the analysis with cilta cel, teclistamab was less costly and less effective.

Table 1 Applicant base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
TPC[b]	75,679	1.13	-	-	-
Teclistamab	271,121	2.65	195,441	1.52	128,269

ICER: incremental cost-effectiveness ratio; **QALY**: quality adjusted life year; **TPC**: Treatment of physician's choice

[a] Corresponding probabilistic ICER using 1,000 iterations =€129,013.86/QALY.

Total costs and QALYS presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable.

[b] A CIC PAS applies to a number of treatments included in the TPC basket of comparator regimens, not included here.

Table 2 Applicant base case incremental cost-effectiveness results – cilta cel analysis[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Cilta cel	388,078	4.22	-	-	-
Teclistamab	278,201	2.35	-109,878	-1.88	Teclistamab is less costly, less effective

ICER: incremental cost-effectiveness ratio; **QALY**: quality adjusted life year.

[a] Total costs and QALYS presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable.

Table 3 NCPE adjusted base case incremental cost-effectiveness results[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
TPC[b]	75,025	1.27	-	-	-
Teclistamab	277,524	2.35	202,499	1.07	188,452

TPC: Treatment of physician's choice; **QALY**: Quality adjusted life years; **ICER**: Incremental cost-effectiveness ratio

[a] Corresponding probabilistic ICER using 1,000 iterations =€189,206/QALY. Total costs and QALYS presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable.

[b] A CIC PAS applies to a number of treatments included in the TPC basket of comparator treatments, not included here.

Table 4 NCPE adjusted base case incremental cost-effectiveness results – cilta cel analysis[a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Cilta cel	388,141	3.71	-	-	-
Teclistamab	278,201	2.35	-109,940	-1.37	Teclistamab is less costly, less effective

QALY: Quality adjusted life years; **ICER**: Incremental cost-effectiveness ratio

[a] Total costs and QALYS presented are discounted (4%). Figures in the table are rounded, and so calculations may not be directly replicable

Sensitivity analyses indicated that the main driver of cost-effectiveness in the Applicant base case related to the choice of extrapolation curves for teclistamab (when based on the

Subgroup 1 and Subgroup 2 landmark approach). A Price-ICER analysis, under the NCPE adjusted base case assumptions, indicates that a reduction of about 70% and 81%, in the price-to-wholesaler (PtW) of teclistamab, would be required to meet the €45,000/QALY and €20,000/QALY thresholds respectively.

4. Budget impact of teclistamab

The PtW of teclistamab is €905.00 for one 30mg vial and €4,615.40 for one 153mg vial. The estimated cost of teclistamab per-patient, per-treatment course is €196,983 including valued added tax [VAT] (€157,415 excluding VAT), assuming a treatment duration of 8.5 months from the MajesTEC-1 trial.

The Applicant submitted a budget impact model. Many of the inputs are very uncertain and therefore there is considerable uncertainty associated with the budget impact estimates. The Applicant estimated that 152 patients would receive treatment over five years. The Applicant's estimated five-year cumulative gross drug budget impact for teclistamab is €30 million including VAT (€24 million excluding VAT). The estimated five-year cumulative net drug budget impact is €23.2 million including VAT (€18.2 million excluding VAT). The Review Group considers that the true number of patients expected to receive treatment will be higher (as some patients may receive treatment sooner than third line, and market shares for teclistamab, which is a first-in-class treatment, may be underestimated), and thus the Applicant's budget impact estimates are underestimated.

5. Patient Organisation Submission

A patient organisation submission was received from Multiple Myeloma Ireland.

6. Conclusion

The NCPE recommends that teclistamab 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