SMC2668

teclistamab solution for injection (Tecvayli®)

Janssen-Cilag Ltd

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan equivalent medicine process

teclistamab (Tecvayli®) is accepted for use within NHSScotland.

Indication under review: 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.

In a single-arm, phase I/II study in patients with relapsed and refractory multiple myeloma, teclistamab was associated with an overall response rate of 63%.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Teclistamab is a bispecific antibody that targets the CD3 receptors expressed on the surface of T cells and B-cell maturation antigen (BCMA), which is expressed on the surface of malignant multiple myeloma B-lineage cells, as well as late-stage B cells and plasma cells. By binding to both sites, teclistamab is able to draw the T cells closer to the BCMA-expressing cells, which leads to lysis of these cells. The recommended dose of teclistamab is 1.5 mg/kg by subcutaneous injection weekly, preceded by step-up doses of 0.06 mg/kg and 0.3 mg/kg. Patients should be treated with teclistamab until disease progression or unacceptable toxicity. In patients who have a complete response or better for a minimum of 6 months, a reduced dosing frequency of 1.5 mg/kg subcutaneously every two weeks may be considered. For more information on teclistamab dosing, including information on pre-treatments, step-up dosing schedule, and dosing modifications, refer to the Summary of Product Characteristics.[1]

1.2. Disease background

Multiple myeloma is a rare and incurable haematological cancer which mostly affects people over 60 years of age. It is the second most common haematological cancer after non-Hodgkin's lymphoma; in Scotland there are an estimated 477 new cases diagnosed each year. Characteristics of multiple myeloma include osteolytic lesions, anaemia, increased susceptibility to infections, hypercalcaemia, renal insufficiency or failure and neurological complications. Patients typically experience periods of disease control after initial treatment followed by progression, with subsequently shorter disease control periods after each successive treatment. Drug resistance to prior regimens in patients with relapsed or refractory multiple myeloma is due to continuous changes in the disease biology, in which a higher proportion of malignant cells are expressing a more aggressive, highly proliferative phenotype over time. Patients with multiple myeloma have a poor prognosis; median overall survival in patients who have received at least three prior lines of therapy and are refractory to both an immunomodulatory agent and a proteasome inhibitor is 13 months.[2, 3]

1.3. Treatment pathway and relevant comparators

In recent years, several new medicines have become available for patients with relapsed and refractory multiple myeloma and the treatment pathway is evolving. Treatment choice is influenced by many factors such as patient preference, age, cytogenetic profile, comorbidities, performance status, and most importantly the type of therapies previously received and response to these.[3, 11, 14] There may also be geographical variation in prescribing patterns in Scotland. Patients earlier in the treatment pathway may receive combinations of immunomodulatory agents (such as lenalidomide or thalidomide), proteasome inhibitors (such as bortezomib) or anti-CD38 antibodies (such as daratumumab) in conjunction with dexamethasone. There are several potential treatment options for patients 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. These include lenalidomide plus dexamethasone, pomalidomide plus dexamethasone, isatuximab plus pomalidomide plus dexamethasone, carfilzomib plus dexamethasone, panobinostat plus bortezomib plus

dexamethasone, and daratumumab monotherapy. Clinical experts consulted by SMC identified several potentially relevant comparators including isatuximab plus pomalidomide plus dexamethasone, pomalidomide plus dexamethasone, daratumumab monotherapy and bendamustine.

1.4. Category for decision-making process

Eligibility for interim acceptance decision option

Teclistamab received an Innovation Passport allowing entry into the Innovative Licensing and Access Pathway and has conditional marketing authorisation from the Medicines and Healthcare Products Regulatory Agency.

Eligibility for a PACE meeting

Teclistamab meets SMC end of life and orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of teclistamab comes from MajesTEC-1. See Table 2.1 for details.

Table 2.1. Overview of relevant study[3, 4]

Criteria	MajesTEC-1 study
Study design	Open-label, single arm, multicentre, non-randomised, phase I/II study.
Eligible patients	• At least 18 years of age • Documented diagnosis of relapsed or refractory multiple myeloma according to International Myeloma Working Group diagnostic criteria[10] • Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1 • Previously received at least three lines of therapy (including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody) • Progressive, measurable disease at screening
Treatments	Teclistamab 1.5 mg/kg once weekly via subcutaneous injection, preceded by step-up doses of 0.06 mg/kg and 0.3 mg/kg. Teclistamab was given until disease progression, unacceptable toxicity, withdrawal of consent, death, or end of study.
Randomisation	Not applicable.
Primary outcome	Overall response rate, defined as partial response or better as assessed by independent review committee based on International Myeloma Working Group criteria.[10]
Secondary outcomes	Duration of response, time to response, progression-free survival, overall survival, time to next treatment, minimal residual disease.
Statistical analysis	Efficacy and safety were analysed in all patients who had received at least one dose of teclistamab at the recommended phase II dose (described above), either in phase I or phase II of the study. Time-to-event outcomes were estimated using Kaplan-Meier methods.

After a median follow-up of 30.4 months (August 2023 data-cut off), the overall response rate was 63%.[5] See Table 2.2 for more details.

Table 2.2. Key efficacy results from MajesTEC-1 (All-treated analysis set).[3, 4, 5]

	Teclistamab (n=165)	
Data-cut	**March 2022**	**August 2023**
Primary outcome: overall response rate (IRC-assessed as per IMWG criteria)		
Median follow-up	14.1 months	30.4 months
ORR	63%	63%
Stringent CR	33%	39%
CR	6.7%	7.3%
Very good PR	19%	13.3%
PR	4.2%	3.6%
Secondary outcome: duration of response (IRC-assessed as per IMWG criteria)		
	n=104**	*
Number of events	33	55
Median DOR	18.4 months	24.0 months
12-month event-free rate	68%	70%
Secondary outcome: progression-free survival (IRC-assessed as per IMWG criteria)		
Number of events	*	107
Median PFS	11.3 months	11.4 months
12-month PFS rate	48%	49%
Secondary outcome: overall survival (IRC-assessed)		
Number of events	*	94
Median OS	18.3 months	22.2 months
9-month OS rate	77%	75%

** Based on the number of responders from the all-treated analysis set.

*Other data were also assessed but remain confidential.**

Abbreviations: CR = complete response; DOR = duration of response; IMWG = International Myeloma Working Group; IRC = independent review committee; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response.

2.2. Health-related quality of life outcomes

Health-related quality of life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), EQ-5D-5L, and Patient Global Impression questionnaires. Meaningful improvement from baseline at cycles two, four, and six was reported by up to 36% of patients for global health status (EORTC QLQ-C30). Meaningful (7-point) improvement from baseline in visual analogue scale scores was reported by 24%, 29%, and 30% of patients respectively at cycles two, four, and six (EQ-5D-5L). At baseline, 14% of patients reported disease severity of none or mild; at cycles two, four, and six, 26%, 48%, and 55% of patients respectively reported disease severity of none or mild (Patient Global Impression) (all HRQoL results taken from March 2022 data-cut).[3]

2.3. Supportive studies

Riedhammer et al. (2024) was an observational retrospective analysis of teclistamab in 123 patients with relapsed and refractory multiple myeloma from 18 centres in Germany. Patients in this analysis had different baseline characteristics than in MajesTEC-1; patients were older (median age 67 years versus 64 years), had a higher median number of lines of prior therapy (6 versus 5), and a higher proportion were triple-class refractory (93% versus 78%). Despite these differences, teclistamab appeared to exhibit similar efficacy in the real-world analyses compared with MajesTEC-1 (ORR in 59% of patients).[9]

Dima et al. (2023) reported a retrospective analysis of teclistamab in 102 patients with relapsed and refractory multiple myeloma from 5 academic centres in the USA. More than 80% of patients in this study would not have been eligible for MajesTEC-1 due to receiving prior BCMA-targeted therapy (55%), ECOG performance status ≥2 (28%) or baseline cytopenias. After a median follow-up of 3.2 months, the ORR was 64%.[11]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing teclistamab with relevant comparators, the submitting company presented an indirect treatment comparison versus pomalidomide plus dexamethasone (Table 2.3).

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Unanchored, adjusted ITC was applied using IPTW to estimate the ATC. The ATC was selected so that the characteristics of the single arm pivotal study, MajesTEC-1, could be re-weighted to mimic those of the UK RW TCE cohort study, and therefore, the population of relevance to this submission.
Population	Triple class exposed (proteasome inhibitor, immunomodulatory agent, and anti-CD38 antibody) relapsed and refractory multiple myeloma with an Eastern Cooperative Oncology Group performance score of 0–1, aged 18 years or over.
Comparators	Pomalidomide plus dexamethasone.
Studies included	MajesTEC-1 and the UK RW TCE cohort study[12, 13]
Outcomes	OS and TTNT (which acted as a proxy for PFS in the economic model)
Results	Treatment with teclistamab resulted in a statistically significant improvement in TTNT (HR 0.56, 95% CI 0.40 to 0.79) and OS (HR 0.52, 95% CI 0.36 to 0.74).

Abbreviations: ATC, average treatment effect of the control; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability treatment weights; ITC, indirect treatment comparison; OS, overall survival; PFS, progression free survival; PomDex, pomalidomide plus low-dose dexamethasone; TCE, triple class exposed (proteasome inhibitor, immunomodulatory agent, and anti-CD38 antibody); RRMM, relapsed and refractory multiple myeloma; TTNT, time to next treatment; UK RW TCE, United Kingdom Real World Triple Class Exposed cohort

3. Summary of Safety Evidence

In the MajesTEC-1 study at data-cut March 2022, the median duration of treatment was 8.5 months. In the all-treated analysis set (n=165), any treatment emergent adverse event (AE) was reported by 100% of patients, and 93% were considered related to teclistamab; any serious treatment emergent AE was reported by 65%, and 29% were considered related to teclistamab. There were 2 (1.2%) treatment emergent AEs that led to discontinuation of study medicine, and 27 (16%) treatment emergent AEs with outcome of death; 7.3% were due to COVID-19. The most common treatment emergent AEs reported in MajesTEC-1 (in at least 20% of the all-treated analysis set) were neutropenia (71%), anaemia (52%), thrombocytopenia (40%), lymphopenia (34%), pyrexia (27%), fatigue (28%), cytokine release syndrome (CRS) (72%), arthralgia (22%), back pain (16%), diarrhoea (28%), nausea (27%), cough (20%), headache (24%). Regulatory bodies consider CRS, neurological toxicity, and infections to be the key risks of teclistamab. CRS AEs appeared to be transient in nature, mostly low-grade severity, and overall manageable. Infections are common in patients with relapsed/refractory multiple myeloma due to underlying immunosuppression, however teclistamab causes neutropenia and hypogammaglobulinaemia and therefore increases the risk of infection. Immune effector cell-associated neurotoxicity syndrome (ICANS) was reported in 3.0% of patients who received the licensed dose of teclistmab. Although currently available data enable a reasonable characterisation of the safety profile of teclistamab, the lack of a control group in MajesTEC-1 is limiting.[3, 4]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Teclistamab is a bispecific antibody that targets both CD3 and BCMA receptors. This class of medicine is distinct from other available multiple myeloma treatments and offers a new mechanism of action.
- In MajesTEC-1, teclistamab demonstrated a clinically relevant anti myeloma effect in a population with a history of several prior treatments and refractory disease; 63% of patients had a response to treatment, with 46% at latest data-cut having a complete response or better. The depth and duration of response were also considered supportive and clinically relevant.[3, 4]

4.2. Key uncertainties

- MajesTEC-1 was a single-arm, open-label, phase I/II study, which are prone to various biases such as selection bias. The treatment effect of teclistamab relative to relevant comparators in clinical practice is therefore uncertain. The submitting company presented an indirect comparison versus pomalidomide plus dexamethasone, however there are

numerous potentially relevant comparators that were not included in the indirect treatment comparison. Given the evolving treatment pathway, the heterogeneity of treatment selection, and the potential for geographical variation it is challenging to identify the most relevant comparators.

- ORR is an appropriate outcome in phase II studies that measures anti-tumour activity. However, it may be unclear to what degree this anti-tumour activity corresponds to more robust measures of clinical benefit, such as overall survival (OS) or progression-free survival (PFS). It is difficult to interpret the OS and PFS data from MajesTEC-1 due to the single-arm, non-randomised design of the study, and is further complicated by deaths caused by the COVID-19 pandemic.[3]
- There was a limited sample size (n=165) in the key study. However, this may be expected in an orphan equivalent condition such as relapsed and refractory multiple myeloma.[3]
- The HRQoL outcomes evaluated in MajesTEC-1 should be interpreted cautiously given the open-label design of the study.[3]
- There may be differences between the study population of MajesTEC-1 and the Scottish population. Patients in MajesTEC-1 were likely fitter and younger than relevant patients in Scotland, however the number of patients in the study with triple-class refractory disease (approximately 78%) may be higher than that expected in the eligible Scottish patient population.
- The indirect treatment comparison versus pomalidomide plus dexamethasone had the following limitations:
    - Unanchored indirect comparisons are inherently uncertain and susceptible to confounding bias due to differences in unobserved or observed characteristics that were not adjusted for.
    - Comparisons based on real-world data versus clinical study data may be prone to bias as patients may respond better to treatment in a trial setting than in clinical practice and the quality of data collection may be poorer in real-world studies and may introduce error.
    - Wide confidence intervals indicate uncertainty in the results.
    - Safety and health-related quality of life were not assessed due to data not being available from the real-world observational study.

  Due to these limitations, the magnitude of benefit of teclistamab versus pomalidomide plus dexamethasone is uncertain.

4.3. GB/EMA conditional marketing authorisation specific obligations

The MHRA specific obligations include the submission of the final study report of MajesTEC-1 (August 2023 data-cut) and also results for MajesTEC-3, a randomised phase III study comparing teclistamab in combination with daratumumab versus comparators, which is not relevant to the indication under review. Therefore, the obligations will not address the key uncertainties identified in the clinical evidence presented.

4.4. Clinical expert input

Clinical experts consulted by SMC considered that teclistamab fills an unmet need in this setting and consider it to be a therapeutic advancement as it is a new class of medicine that has shown to be effective in heavily pre-treated patients.

4.5. Service implications

Clinical experts consulted by SMC considered that the introduction of this medicine will have substantial implications for the service. Extensive monitoring is required, and in-patient admission may be required to initiate treatment due to the potential for CRS or ICANS. There may be an advantage for the service and patient once treatment is established as it is administered subcutaneously. Clinical experts consulted by SMC also considered that a high proportion of patients that receive a bispecific antibody may require concomitant IV immunoglobulin to prevent infection, which could also have important implications for the service.

5. Patient and Clinician Engagement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of teclistamab, as an **orphan-equivalent/end of life** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Myeloma is a severe, incurable, relapse-remitting disease that can develop at any age but is more common in people over the age of 60. While myeloma is a highly individual and complex cancer, common symptoms include bone pain, bone destruction, back pain, fatigue, kidney damage, a depleted immune system, and generalised weakness. As patients progress through subsequent treatments in the relapsed/refractory setting, many patients will also experience intensified side effects, which have a higher physical and psychological burden. Myeloma has a marked impact on people's mental and physical health, as well as their quality of life. Fear of the unknown is often highlighted by patients and carers, and the constant possibility of relapse has a huge psychological impact on patients. The physical and psychcological impact increases with every relapse. Patients are aware that every time they relapse, their options and life expectancy decrease. Ongoing symptoms and its various manifestations also affect a patient's ability to work, which may lead to financial worries, and to function well at home. A weakened immune system can also prevent people from partaking in activities previously enjoyed, including exercising, socialising, and travelling. This, alongside the need for frequent hospital visits, can result in a significantly reduced quality of life.
- In the past decade a wide range of treatments have been made available for treating relapsed and refractory myeloma which offer significant improvements in survival. However, myeloma is incurable, and even if remission is achieved with current treatments, patients know that they will relapse at an unknown point in the future. Currently available treatments are seen to provide reasonable responses in a minority, however for many the responses are not durable or are only "partially successful". Currently available treatments also have side effects associated with them which can have a physical and psychological toll. Steroids are commonly

prescribed as part of treatment regimens, and can cause mood swings, irritability, and mania which is challenging for patients and their families. Given that myeloma evolves over time and becomes resistant to treatment, patients can quickly cycle through and run out of treatments options despite still being fit to receive further treatment. Therefore, there is a clear unmet need for new, well-tolerated treatments for the treatment of relapsed and refractory multiple myeloma.

- There are numerous benefits to support the introduction of teclistamab to clinical practice in Scotland. Teclistamab has the potential to greatly improve quality of life and overall life expectancy. Study data shows that teclistamab offers high response rates compared to what has historically been reported with other treatments, durable responses, disease control, and promising life expectancies which are all highly valued by patients. This treatment could allow patients to enjoy a normal day-to-day life. Patients could continue in work or education, and quality of life could be greatly improved by improving symptoms such as fatigue. Teclistamab has a novel mechanism of action. If approved, it would be the first T-cell engager and the first B cell maturation antigen (BCMA) targeted treatment for myeloma. Therefore, it has much potential to overcome treatment resistance and fulfil an unmet need for relapsed/refractory multiple myeloma patients. If approved, there would be a psychological benefit of knowing that another treatment is available should patients relapse. The value of hope offered by teclistamab eases the emotional burden which patients with relapsed and refractory multiple myeloma and their families experience. Furthermore, having different choices for treatment is desirable for patients. Teclistamab is administered as a monotherapy. Patients welcome not having to take concomitant steroids alongside teclistamab, which have considerable side effects and have likely featured in past treatment regimens for multiple myeloma.
- Carers and family members play a critical role in patients' disease and treatment journey and caring for someone with relapsed and refractory multiple myeloma is often very challenging and burdensome. Teclistamab is expected to provide durable responses for patients, which should lead to a reduction in dependency on family members and carers. Teclistamab has the potential to give families longer, quality time together. The fear of relapse and the uncertainty associated with limited treated options is experienced by patients and families/carers alike, and the availability of teclistamab should have a positive psychological benefit for people who are close to the person with myeloma. The absence of dexamethasone is also expected to have a huge impact on carers, partners, and families. The changing mood and fluctuating energy levels patients experience when taking dexamethasone has a significant impact on their relationships and family dynamics. There may be an additional benefit for carers to deliver teclistamab in a healthcare setting as carers can feel a lot of responsibility to support and monitor patients at home with alternative treatments.
- Teclistamab is an effective treatment option for those who have triple-class exposed relapsed and refractory multiple myeloma, however there are some side effects associated with the treatment including CRS, hypogammaglobulinaemia, and increased risk of infections which can be a cause for concern for patients and their loved ones. However, patients are aware that these side effects typically occur when starting treatment, and they felt there were similar risks associated with other treatments. PACE participants felt that the adverse events associated with teclistamab are manageable, and that the risk of severe CRS and ICANS

toxicities was low. Toxicities such as CRS are not unique to teclistamab and clinicians are experienced in the management of such adverse events.

- There may also be service implications associated with the introduction of teclistamab due to close monitoring of side effects, increased resource required from specialist centres (at least initially), and the high likelihood of patients requiring prophylactic antibiotics/antivirals and IV immunoglobulins to prevent infection.

Additional Patient and Carer Involvement

We received patient group submissions from Myeloma UK and Blood Cancer UK, which are both registered charities. Myeloma UK has received 5.65% pharmaceutical company funding in the past two years, including from the submitting company. Blood Cancer UK has received 1.6% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from Myeloma UK and Blood Cancer UK participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	40 years.
Population	The submitting company requested SMC consider teclistamab for the treatment of adult patients with 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.
Comparators	Pomalidomide plus dexamethasone.
Model description	A three-state partitioned survival analysis was used, with health states of progression free, progressed disease and death. All patients entered the model in the progression free health state, receiving treatment with either teclistamab or pomalidomide plus dexamethasone, and remained in this health state until disease progression or death. Patients receiving teclistamab could switch from a weekly to a 2-weekly administration of teclistamab. Treatments were discontinued at, or prior to, progression. In the progressed disease health state, patients either remained in this health state or transitioned to the death state. Subsequent treatments were administered in this health state. Death was an absorbing health state. A one-week cycle length was used.
Clinical data	OS, time to next treatment (as a proxy for PFS) (TTNT) and time to treatment discontinuation (TTD) data from MajesTEC-1 (August 2023 data-cut off) were used for teclistamab.[3, 4, 5] Additional data from MajesTEC-1 were dose-switching data (weekly to 2-weekly) and the proportion of missed doses for teclistamab. OS and TTNT (as a proxy for PFS) data for pomalidomide plus dexamethasone were from the United Kingdom real world triple class exposed cohort study (January 2013 to March 2023) (UK RW TCE cohort study). Grade 3 and higher adverse events that had occurred in at least 5% of patients for either teclistamab (in the MajesTEC-1 study) or pomalidomide plus dexamethasone (in the MM-003 study) were included.
Extrapolation	OS, TTNT (as a proxy for PFS) and TTD data were extrapolated independently in each treatment arm.

	Teclistamab OS and TTNT data were both extrapolated using the log-normal distribution, with TTD data extrapolated using the gamma distribution. Prior to extrapolation, the MajesTEC-1 TTNT and OS Kaplan–Meier data were adjusted using inverse probability treatment weights (IPTW) based on average treatment effect of the control (ATC) weights from the indirect treatment comparison. In addition, extrapolated OS outcomes were adjusted for subsequent treatment not routinely available in UK clinical practice. Long term (10 and 15 year) OS and TTNT (as a proxy for PFS) outcomes were adjusted using company clinical expert calibration. A Gompertz extrapolation was also fitted to the dose switching Kaplan–Meier data to smooth out the stepwise nature of these data. Pomalidomide plus dexamethasone OS and TTNT data were extrapolated using the Gompertz distribution. No pomalidomide plus dexamethasone TTD data were available in the UK RW TCE cohort study. Hence, the relative difference between teclistamab TTNT and teclistamab TTD was calculated; the resulting hazard ratio was then applied to the Gompertz pomalidomide plus dexamethasone TTNT extrapolation to derive a TTD extrapolation.
Quality of life	The base case used treatment-dependent health state utility values for PFS and progressed disease (i.e., utility values were different depending on the health state and treatment). Teclistamab utility values were derived from the EQ-5D-5L data from MajesTEC-1. The PFS health state used time-dependent utility values. These were higher the longer the time spent in the progression free health state. Pomalidomide plus dexamethasone utility values were informed by the MM-003 study in SMC1205/17. These were 0.610 in the PFS health state and 0.570 in the progressed disease health state. Adverse event disutilities were included as a one-off utility decrement. Health state utility values were age-adjusted.
Costs and resource use	Drug acquisition, administration, adverse event management (including immunoglobulin costs for hypogammaglobulinemia), co-medication, subsequent treatments, monitoring, and end-of-life palliative care were included. The base case included a proportion missed teclistamab doses. Resource use was sourced from the summary of product characteristics and previous UK health technology appraisals.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. A PAS discount is in place for pomalidomide and this was included in the results used for decision-making by using estimates of the comparator PAS price. The results presented do not take account of the PAS for teclistamab or the PAS for pomalidomide but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for pomalidomide due to commercial confidentiality and competition law issues.

6.2. Results

The base case results are presented in Table 6.2 Results in Table 6.2 use list prices for all medicines.

Table 6.2: Deterministic base-case results (List prices)

Teclistimab versus:	**ICER (£/QALY)**
PomDex	51,971

Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years; PomDex = pomalidomide plus dexamethasone

6.3. Sensitivity analyses

The base case results were most sensitive to a shortened time horizon, alternative utility values, long term clinical calibration estimates, the proportion of missed doses, and alternative teclistamab TTD extrapolations. Results in Table 6.3 use list prices for all medicines.

Table 6.3: Scenario analysis results (List prices)

	Parameter	**Base case**	**Scenario**	**ICER (£/QALY)**
	Base case	-	-	**51,971**
1	Time horizon	40 years	10 years	59,505
2	OS Teclistamab extrapolation	Lognormal	Weibull	54,605
3	OS PomDex extrapolation	Gompertz	Weibull	50,954
4	PFS Teclistamab extrapolation	Lognormal	Weibull	53,287
5	PFS Teclistamab data	Use of TTNT as proxy for PFS	Use PFS IRC	51,253
6	PFS PomDex extrapolation	Gompertz	Exponential	52,102
7	TTD Teclistamab extrapolation	Gamma	Lognormal	71,360
8	TTD PomDex extrapolation	HR (PFS and TTD for teclistamab) applied to PomDex PFS	PomDex Gompertz PFS PomDex	40,169
9	Subsequent treatment adjustment (OS Teclistamab)	Include	Exclude	49,692
10a	Teclistamab OS and PFS long term clinical calibration	Median (OS 10 year 10% 15 year 3%. PFS 10 year 5% 15 year 1%)	Lower limit	61,727
10b			Upper limit	45,495
11a	Utility values	Treatment-dependent and TEC PFS time dependent	Treatment independent and PFS time dependent	57,642
11b			Treatment independent and time independent	60,044
12	Dose Switching (weekly to 2-weekly)	Gompertz extrapolation	100% on treatment switch at Year 1 exactly.	50,749
13a	Missed doses proportion	Expected doses as per licensed wording	Switching to 2-weekly, monthly and 2-monthly schedules do not incur missed doses.	54,958
13b			Exclude missed doses (0%)	76,585
14	Teclistamab hospital bed days	4 days (first week) 2 days (second week)	5 days (first week) 5 days (second week)	53,979

Abbreviations: HR = hazard ratio; ICER = incremental cost-effectiveness ratio; Incr. = incremental; IRC = independent review committee; OS = overall survival; PD = progressed disease; PFS = progression free survival; PomDex = pomalidomide plus dexamethasone; QALYs =quality-adjusted life years; TEC = teclistamab; TTD = time to treatment discontinuation; TTNT = time to next treatment.

6.4. Key strengths

- The model structure was appropriate to capture disease progression for patients receiving treatment for RRMM.
- The survival analysis was conducted in accordance with NICE Decision Support Unit Technical Support Document 14.[14]
- A comprehensive selection of parameters considered in one-way deterministic scenario analysis.

6.5. Key uncertainties

- SMC clinical experts highlighted a broader selection of displaced comparators than the submitting company. In addition to pomalidomide plus dexamethasone, SMC clinical experts highlighted that daratumumab monotherapy, isatuximab plus pomalidomide and dexamethasone, and bendamustine would be likely to be displaced by the introduction of teclistamab. There were no economic results available against these comparators in the company submission, with requested additional exploratory analysis unavailable.
- The base case time horizon of 40 years was subject to uncertainty. Given the poor prognosis of triple class exposed RRMM, a shortened 10-year time horizon may be a more reasonable consideration (scenario 1), increasing the ICER.
- There was uncertainty in the approach used for utility values. In the base case treatment-dependent utility values were used, with the submitting company noting the distinct mechanism of action between teclistamab and pomalidomide plus dexamethasone leading to differentiated depths of response and resulting improvements in health-related quality of life.[15] However, the utility values for pomalidomide plus dexamethasone were not drawn from a triple class exposed RRMM population, and previous SMC submissions for RRMM (SMC 2303 and SMC972/14) have used treatment-independent utilities. In addition, the time-dependent progression free utilities used for teclistamab were subject to issues of face validity as utility values at the last timepoints exceeded general UK population values.[16] Scenario 11a considers using treatment independent utilities from MajesTEC-1 and scenario 11b considers applying treatment and time-independent utilities from MajesTEC-1, both increasing the ICER.
- There was uncertainty in the generalisability to NHS Scotland of the missed doses proportion applied in the model. Although the base case figures derived from the MajesTEC-1 data may be applicable to practice, SMC experts stated mixed views on the appropriateness of the figure used in the base case. Given this uncertainty, a scenario was considered that conservatively excluded the missed doses proportion, increasing the ICER (Scenario 13b).

- Limitations of the ITC increased uncertainty in the economic results. Given that the OS and TTNT data (as a proxy for PFS) from MajesTEC-1 were adjusted to match the UK RW TCE cohort study prior to performing extrapolations, limitations in the ITC methods increased uncertainty in extrapolated health outcomes. Although the ITC matching adjustments appeared to be conservative for teclistamab OS and TTNT outcomes, with an additional scenario to show limited ICER impact when considering an unadjusted analysis, multiple ITC limitations were identified which generated uncertainty in the comparative efficacy of teclistamab and pomalidomide plus dexamethasone.
- Long term OS and PFS (using TTNT as a proxy) outcomes for teclistamab were adjusted using clinical calibration. This rested on assumptions of the appropriate time points of application, and the choice of which long-term clinical expert survival estimates to apply. These estimates were inherently subject to uncertainty, given there no long-term use of teclistamab in practice. Scenario analysis highlighted ICER variation when using the lower and upper limits of clinician estimates at 10 and 15 years (scenarios 10a and 10b).
- There was uncertainty in the TTD extrapolation in the teclistamab arm. The base case gamma distribution was selected as it fitted within the bounds of the company clinical expert estimates. However, the lognormal extrapolation aligned with the median of the company clinical experts at 5 years and was only slightly above the upper bound of company clinical estimates at 10 and 15 years. Given there is no long-term use of teclistamab in practice and long-term treatment estimates are subject to uncertainty estimates, the use of the lognormal shows a more conservative approach to teclistamab acquisition costs (scenario 7).
- There was uncertainty in the proportion of patients in the teclistamab arm that would receive IVIG treatment. In general, SMC clinical experts highlighted that at least 75% of teclistamab patients would receive IVIG treatment under current guidelines. Additional sensitivity analysis showed that raising the proportion of patients receiving IVIG increased the ICER, although it was not possible to capture wider interactions such as impacts on the duration of treatment and the relative treatment efficacy of teclistamab.
- There was uncertainty in the number of hospital bed days required for teclistamab initiation. SMC clinical experts highlighted that teclistamab may require approximately 10 hospital bed days at initiation. Increasing the number of hospital days at initiation increased the ICER (scenario 14).
- There was uncertainty in the use of TTNT data as a proxy for PFS. To support this in the teclistamab arm, the submitting company provided TTNT and PFS Kaplan-Meier curves from MajesTec-1, demonstrating a very similar trajectory over time, with a scenario showing a limited ICER impact (scenario 5). However, as no PFS data were available for comparison with the TTNT data from the UK RW TCE cohort study in the PomDex arm it remains unknown whether the TTNT and PFS trajectories would be similar, with the impact on economic results of using PFS data in the PomDex arm unknown.

*Other data were also assessed but remain confidential.**

7. Conclusion

The Committee considered the benefits of teclistamab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as teclistamab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted teclistamab for use in NHSScotland.

8. Guidelines and Protocols

The British Society for Haematology (BSH) published "Guidelines on the diagnosis, investigation and initial treatment of myeloma: a British Society for Haematology/UK Myeloma Forum Guideline" in March 2021.[6]

The National Institute for Health and Care Excellence (NICE) published "Myeloma: diagnosis and management" (NG35) in February 2016, which was updated in October 2018.[7]

The European Society for Medical Oncology (ESMO) and the European Haematology Association (EHA) published "Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up" in February 2021.[8]

9. Additional Information

9.1. Product availability date

03 February 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 28 days (£)
Teclistamab	**1.5 mg/kg once weekly via subcutaneous injection, preceded by step-up doses of 0.06 mg/kg and 0.3 mg/kg. In patients who have a complete response or better for a minimum of 6 months, the patient may be given 1.5 mg/kg every 2 weeks.**	**£12,402 (not including step-up doses; weekly dosing)** **£6,201 (not including step-up doses; 2-weekly dosing)**

Costs from BNF online on 01 May 2024. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs assume a body weight of 70 kg. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 56 patients eligible for treatment with teclistamab in year 1 and 57 in year 5, to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to

estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 21 June 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.