PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTALVEY™

talquetamab injection

3 mg/1.5 mL (2 mg/mL) solution for subcutaneous injection

40 mg/1.0 mL (40 mg/mL) solution for subcutaneous injection

Professed Standard

Antineoplastic, monoclonal antibody

ATC code: L01FX29

Talvey, indicated for:

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

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for Talvey please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html

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Date of Initial Authorization:
APR 30, 2024

Submission Control Number: 278277

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

RECENT MAJOR LABEL CHANGES

Not applicable.

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TALVEY™ (talquetamab injection) is indicated for:

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

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years of age): Of the 339 patients treated with Talvey in MonumenTAL-1, 36% were 65 to less than 75 years of age, and 17% were 75 years of age or older. No clinically important differences in safety or effectiveness were observed in patients 65 to 75 years of age compared to younger patients. There are limited clinical data with talquetamab in patients 75 years of age or over. No dose adjustment is required (see 10.3 Pharmacokinetics).

2 CONTRAINDICATIONS

Talvey is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Cytokine release syndrome (CRS), including life-threatening or fatal reactions, can occur in patients receiving Talvey. Initiate Talvey treatment with step-up dosing to reduce the risk of CRS. Monitor patients for signs and symptoms of CRS. Withhold Talvey and provide supportive care and treatment until CRS resolves or permanently discontinue based on severity. (See 4.2 Recommended Dose and Dosage Adjustment - Dose modifications for adverse reactions and 7 WARNINGS AND PRECAUTIONS - CRS)
- Neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), including serious or fatal reactions, have occurred following treatment with Talvey. Monitor patients for signs and symptoms of neurologic toxicity, including ICANS and treat promptly. The onset of ICANS may be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Withhold Talvey until the neurologic toxicity resolves or discontinue based on severity. (See 4.2 Recommended Dose and Dosage Adjustment - Dose modifications for adverse reactions and 7 WARNINGS AND

PRECAUTIONS - ICANS)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Counsel potential Talvey patients on the risks of CRS and neurologic toxicity, including ICANS and provide patients with the Patient Card.
- Talvey is administered via subcutaneous injection.
- Talvey should be administered by a healthcare professional, experienced in the treatment of multiple myeloma, with appropriate medical support to manage severe reactions, including CRS and neurologic toxicity, including ICANS (see 7 WARNINGS AND PRECAUTIONS). Additional Talvey educational materials for healthcare professionals are available.
- Verify the pregnancy status of females of child-bearing potential prior to initiating Talvey.
- Do not initiate treatment with Talvey in patients with active infection.
- Prior to initiating treatment with Talvey, prophylactic antimicrobials (e.g., prevention of pneumocystis jirovecii pneumonia) and antivirals (e.g., prevention of herpes zoster reactivation) should be considered per local institutional guidelines.
- Administer pretreatment medications prior to each dose of Talvey during the step-up phase (see 4.4 Administration - Pretreatment medications).

4.2 Recommended Dose and Dosage Adjustment

Recommended dose

Administer Talvey subcutaneously on a weekly OR biweekly (once every 2 weeks) dosing schedule according to the corresponding schedule in Table 1.

Table 1: Recommended Dose of Talvey

Dosing schedule	Phase	Day	Talvey Dose[a]	
Weekly Dosing Schedule	Step-up Phase	Day 1	Step-up dose 1	0.01 mg/kg
		Day 4[b]	Step-up dose 2	0.06 mg/kg
		Day 7[b]	First treatment dose	0.4 mg/kg
	Treatment Phase	Once a week thereafter[c]	Subsequent treatment doses	0.4 mg/kg
Biweekly (Every 2 Weeks) Dosing Schedule	Step-up Phase	Day 1	Step-up dose 1	0.01 mg/kg
		Day 4[b]	Step-up dose 2	0.06 mg/kg
		Day 7[b]	Step-up dose 3	0.4 mg/kg
		Day 10[d]	First treatment dose	0.8 mg/kg
	Treatment Phase	Once every 2 weeks thereafter[c]	Subsequent treatment doses	0.8 mg/kg

[a] Based on actual body weight.
[b] Dose may be administered between 2 to 4 days after the previous dose and may be given up to 7 days after the previous dose to allow for resolution of adverse reactions.
[c] Maintain a minimum of 6 days between weekly doses and a minimum of 12 days between biweekly (every 2 weeks) doses.
[d] Dose may be administered between 2 to 7 days after step-up dose 3.

Instruct patients to remain within proximity of a healthcare facility and monitor patients for 48 hours after the administration of each dose during the Talvey step-up phase. Monitor patients for signs and symptoms of CRS and/or ICANS. Alternatively, consider monitoring patients in hospital for 48 hours after each step-up dose (see 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS).

Continue treatment until disease progression or unacceptable toxicity.

Dose modifications for adverse reactions

Dose delays may be required to manage toxicities related to Talvey (see 7 WARNINGS AND PRECAUTIONS).

See Table 2, Table 3, and Table 4 for recommended actions for the management of CRS, ICANS, and neurologic toxicities, respectively. See Table 5 for recommended dose modifications for other adverse reactions.

Cytokine release syndrome (CRS)

Identify CRS based on clinical presentation (see 7 WARNINGS AND PRECAUTIONS - CRS). Evaluate and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, withhold Talvey until CRS resolves, and manage according to the recommendations in Table 2 and consider current practice guidelines. Administer supportive therapy for CRS, which may include intensive care for severe or life-threatening CRS. Consider laboratory testing to monitor for disseminated intravascular coagulation (DIC), hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function.

Table 2: Recommendations for Management of CRS

CRS Grade[a]	Talvey Actions	Tocilizumab[b]	Corticosteroids[c]
Grade 1 Temperature ≥38°C [c]	Withhold Talvey until CRS resolves. Administer pretreatment medication prior to next dose of Talvey.	May be considered.	Not applicable
Grade 2 Temperature ≥38°C [d] with either: • Hypotension responsive to fluids and not requiring vasopressors, or • Oxygen requirement of low-flow nasal cannula[e] or blow-by.	Withhold Talvey until CRS resolves. Administer pretreatment medications prior to next dose of Talvey. Monitor patient daily for 48 hours following the next dose of Talvey. Instruct patients to remain within proximity of a healthcare facility during daily monitoring.	Administer tocilizumab[c] 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed, if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	If no improvement within 24 hours of starting tocilizumab, administer methylprednisolone 1 mg/kg intravenously twice daily, or dexamethasone 10 mg intravenously every 6 hours. Continue corticosteroid use until the event is Grade 1 or less, then taper over 3 days.
Grade 3 Temperature ≥38°C [d] with either: • Hypotension requiring one vasopressor, with or without vasopressin, or • Oxygen requirement of high-flow nasal cannula[e], facemask, non-rebreather mask, or Venturi mask	<u>Duration < 48 hours</u> Per Grade 2. <u>Recurrent or Duration ≥ 48 hours</u> Permanently discontinue Talvey.	Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed, if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	If no improvement, administer methylprednisolone 1 mg/kg intravenously twice daily or dexamethasone (e.g., 10 mg intravenously every 6 hours). Continue corticosteroid use until the event is Grade 1 or less, then taper over 3 days.

CRS Grade[a]	Talvey Actions	Tocilizumab[b]	Corticosteroids[c]
Grade 4 Temperature ≥38°C [d] with either: • Hypotension requiring multiple vasopressors (excluding vasopressin). • Or, oxygen requirement of positive pressure (e.g., continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, and mechanical ventilation)	Permanently discontinue Talvey.	Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed, if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	As above or administer methylprednisolone 1000 mg intravenously per day for 3 days, per physician discretion. If no improvement or if condition worsens, consider alternate immunosuppressants.[c]

[a] Based on ASTCT grading for CRS (Lee et al 2019).
[b] The recommendations reflect the management of CRS in study MonumenTAL-1. Refer to local or institutional guidelines for the use of tocilizumab in the management of CRS.
[c] Treat unresponsive CRS per institutional guidelines.
[d] Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia as it may be masked by interventions such as antipyretics or anti-cytokine therapy (e.g., tocilizumab or corticosteroids).
[e] Low-flow nasal cannula is ≤6 L/min, and high-flow nasal cannula is >6 L/min.

Neurologic toxicities, including immune effector cell-associated neurotoxicity syndrome (ICANS)

At the first sign of neurologic toxicity, including ICANS, withhold Talvey and consider neurology evaluation. Rule out other causes of neurologic symptoms. Provide supportive therapy, which may include intensive care, for severe or life-threatening neurologic toxicities, including ICANS (see 7 WARNINGS AND PRECAUTIONS - ICANS). Management recommendations for ICANS are summarized in Table 3. Management recommendations for other neurologic toxicities are summarized in Table 4.

Table 3: Recommendations for Management of ICANS

ICANS Grade[a, b]	Concurrent CRS	No Concurrent CRS
Grade 1	Management of CRS per Table 2. Monitor neurologic symptoms.	Monitor neurologic symptoms.

ICANS Grade[a, b]	Concurrent CRS	No Concurrent CRS
ICE[c] score 7-9 or depressed level of consciousness[d]: awakens spontaneously.	Withhold Talvey until ICANS resolves. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 2 ICE[c] score 3-6 or depressed level of consciousness[d]: awakens to voice.	Administer tocilizumab per Table 2 for management of CRS. If no improvement after starting tocilizumab, administer dexamethasone[e] 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until resolution to Grade 1 or less, then taper.	Administer dexamethasone[e] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.
	Withhold Talvey until ICANS resolves. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Monitor patient daily for 48 hours following the next dose of Talvey. Instruct patients to remain within proximity of a healthcare facility during daily monitoring.	
Grade 3 ICE[c] score 0-2 (If ICE score is 0, but the patient is arousable (e.g., awake with global aphasia) and able to perform assessment)	Administer tocilizumab per Table 2 for management of CRS. Administer dexamethasone[e] 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.	Administer dexamethasone[e] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.

ICANS Grade[a, b]	Concurrent CRS	No Concurrent CRS
or depressed level of consciousness[d]: awakens only to tactile stimulus, or seizures[d], either: • any clinical seizure, focal or generalized, that resolves rapidly, or • non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, or raised intracranial pressure: focal/local edema on neuroimaging[d].	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. <u>First Occurrence:</u> Withhold Talvey until ICANS resolves. Monitor patient daily for 48 hours following the next dose of Talvey. Instruct patients to remain within proximity of a healthcare facility during daily monitoring. <u>Recurrent:</u> Permanently discontinue Talvey.	
Grade 4 ICE[c] score 0 (Patient is unarousable and unable to perform ICE assessment) or depressed level of consciousness[d] either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma,	Administer tocilizumab per Table 2 for management of CRS. Administer dexamethasone[e] 10 mg intravenously and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Alternatively, consider administration of methylprednisolone 1000 mg per day intravenously with first dose of tocilizumab, and continue methylprednisolone 1000 mg per day intravenously for 2 or more days.	Administer dexamethasone[e] 10 mg intravenously and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Alternatively, consider administration of methylprednisolone 1000 mg per day intravenously for 3 days; if improves, then manage as above.

ICANS Grade[a, b]	Concurrent CRS	No Concurrent CRS
or seizures[d], either: • life-threatening prolonged seizure (>5 minutes), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings[d]: • deep focal motor weakness such as hemiparesis or paraparesis, or raised intracranial pressure/cerebral edema[d], with signs/symptoms such as: • diffuse cerebral edema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilledema, or • Cushing's triad.	Permanently discontinue Talvey. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. In case of raised intracranial pressure/cerebral edema, refer to local institutional guidelines for management.	

[a] Management is determined by the most severe event, not attributable to any other cause.

[b] ASTCT 2019 grading for ICANS.

[c] If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: **Orientation** (oriented to year, month, city, hospital = 4 points); **Naming** (name 3 objects, e.g., point to clock, pen, button = 3 points); **Following Commands** (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); **Writing** (ability to write a standard sentence = 1 point; and **Attention** (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.

[d] Attributable to no other cause.

[e] All references to dexamethasone administration are dexamethasone or equivalent.

Table 4: Recommendations for Management of Neurologic Toxicity (excluding ICANS)

Adverse Reaction	Severity[a]	Actions
Neurologic Toxicity[a] (excluding ICANS)	Grade 1	• Withhold Talvey until neurologic toxicity symptoms resolve or stabilize.[b]
	Grade 2 Grade 3 (First occurrence)	• Withhold Talvey until neurologic toxicity symptoms improve to Grade 1 or less.[b] • Provide supportive therapy.

Adverse Reaction	Severity[a]	Actions
	Grade 3 (Recurrent) Grade 4	• Permanently discontinue Talvey. • Provide supportive therapy, which may include intensive care.

[a] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

[b] See Table 10 for recommendations on restarting Talvey after dose delays for adverse reactions (see 4.5 Missed Dose).

Other adverse reactions

The recommended dose modifications for other adverse reactions are provided in Table 5.

Table 5: Recommended Dose Modifications for Other Adverse Reactions

Adverse Reaction	Severity	Dose Modification
Serious Infections (see 7 WARNINGS AND PRECAUTIONS - Serious infections)	All Grades	• Do not initiate treatment with Talvey in patients with active infection. • Withhold Talvey in the step-up phase until infection resolves.
	Grade 3-4	• Withhold Talvey during the treatment phase until infection improves to Grade 2 or better.
Cytopenias (see 7 WARNINGS AND PRECAUTIONS - Cytopenias)	Absolute neutrophil count less than 0.5×10^9/L	• Withhold Talvey until absolute neutrophil count is 0.5×10^9/L or higher.
	Febrile neutropenia	• Withhold Talvey until absolute neutrophil count is 1.0×10^9/L or higher and fever resolves.
	Hemoglobin less than 8 g/dL	• Withhold Talvey until hemoglobin is 8 g/dL or higher.
	Platelet count less than 25,000/µL Platelet count between 25,000/µL and 50,000/µL with bleeding	• Withhold Talvey until platelet count is 25,000/µL or higher and no evidence of bleeding.
Oral Toxicity (see 7 WARNINGS AND PRECAUTIONS - Oral toxicity)	All grades	Interrupt Talvey until stabilization or improvement, and consider restarting on modified schedule as follows: • If current dose is 0.4 mg/kg every week, change to 0.4 mg/kg every two weeks • If current dose is 0.8 mg/kg every two weeks, change to 0.8 mg/kg every four weeks
Skin Reactions (see 7 WARNINGS AND PRECAUTIONS - Skin reactions)	Grade 3-4	• Withhold Talvey until adverse reaction improves to Grade 1 or baseline.

Adverse Reaction	Severity	Dose Modification
Other Non-hematologic Adverse Reactions[a] (see 8 ADVERSE REACTIONS)	Grade 3-4	• Withhold Talvey until adverse reaction improves to Grade 1 or baseline.

[a] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03.

Special populations

Pediatrics (<18 years of age)

Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥65 years of age)

No dose adjustment is required in patients over 65 years of age (see 10.3 Pharmacokinetics).

Renal impairment

No formal studies of Talvey in patients with renal impairment have been conducted. Results of population pharmacokinetic analyses indicate that mild or moderate renal impairment did not significantly influence the pharmacokinetics of talquetamab (see 10.3 Pharmacokinetics). No data is available in patients with severe renal impairment.

Hepatic impairment

No formal studies of Talvey in patients with hepatic impairment have been conducted. Results of population pharmacokinetic analyses indicate that mild and moderate hepatic impairment did not significantly influence the pharmacokinetics of talquetamab (see 10.3 Pharmacokinetics). No data is available in participants with severe hepatic impairment.

4.4 Administration

Pretreatment medications

Administer the following pretreatment medications 1 to 3 hours before each dose of Talvey during the step-up phase to reduce the risk of CRS (see 7 WARNINGS AND PRECAUTIONS - CRS).

- Corticosteroid (oral or intravenous dexamethasone, 16 mg or equivalent)
- Antihistamine (oral or intravenous diphenhydramine, 50 mg or equivalent)
- Antipyretics (oral or intravenous acetaminophen, 650 mg to 1000 mg or equivalent)

Administer pretreatment medications to patients who repeat doses within the Talvey step-up phase due to dose delays (Table 10) or for patients who experienced CRS (Table 2).

Administration

Administer Talvey via subcutaneous injection.

Talvey should be administered by a healthcare professional with adequate medical equipment and personnel to manage severe reactions, including cytokine release syndrome (see 7 WARNINGS AND PRECAUTIONS - CRS).

Talvey 2 mg/mL vial and 40 mg/mL vial are supplied as ready-to-use solution for injection that do not need dilution prior to administration.

Do not combine Talvey vials of different concentrations to achieve treatment dose.

Use aseptic technique to prepare and administer Talvey.

Preparation of Talvey

- Refer to the following reference tables to determine the number of vials needed and the volume of Talvey required to deliver the intended dose.
    - Use Table 6 to determine total dose, injection volume, and number of vials required based on the patient's actual body weight for the 0.01 mg/kg dose using Talvey 2 mg/mL vial.

Table 6: 0.01 mg/kg Dose: Injection Volumes Using Talvey 2 mg/mL Vial

	Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial = 1.5 mL)
0.01 mg/kg Dose	35 to 39	0.38	0.19	1
	40 to 45	0.42	0.21	1
	46 to 55	0.5	0.25	1
	56 to 65	0.6	0.3	1
	66 to 75	0.7	0.35	1
	76 to 85	0.8	0.4	1
	86 to 95	0.9	0.45	1
	96 to 105	1.0	0.5	1
	106 to 115	1.1	0.55	1
	116 to 125	1.2	0.6	1
	126 to 135	1.3	0.65	1
	136 to 145	1.4	0.7	1
	146 to 155	1.5	0.75	1
	156 to 160	1.6	0.8	1

- Use Table 7 to determine total dose, injection volume, and number of vials required based on the patient's actual body weight for the 0.06 mg/kg dose using Talvey 2 mg/mL vial.

Table 7: 0.06 mg/kg Dose: Injection Volumes Using Talvey 2 mg/mL Vial

	Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial = 1.5 mL)
0.06 mg/kg Dose	35 to 39	2.2	1.1	1
	40 to 45	2.6	1.3	1
	46 to 55	3	1.5	1
	56 to 65	3.6	1.8	2
	66 to 75	4.2	2.1	2
	76 to 85	4.8	2.4	2
	86 to 95	5.4	2.7	2
	96 to 105	6	3	2
	106 to 115	6.6	3.3	3
	116 to 125	7.2	3.6	3
	126 to135	7.8	3.9	3
	136 to145	8.4	4.2	3
	146 to155	9	4.5	3
	156 to160	9.6	4.8	4

- Use Table 8 to determine total dose, injection volume, and number of vials required based on the patient's actual body weight for the 0.4 mg/kg dose using Talvey 40 mg/mL vial.

Table 8: 0.4 mg/kg Dose: Injection Volumes Using Talvey 40 mg/mL Vial

	Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial = 1.0 mL)
0.4 mg/kg Dose	35 to 39	14.8	0.37	1
	40 to 45	16	0.4	1
	46 to 55	20	0.5	1
	56 to 65	24	0.6	1
	66 to 75	28	0.7	1
	76 to 85	32	0.8	1
	86 to 95	36	0.9	1
	96 to 105	40	1	1
	106 to 115	44	1.1	2
	116 to 125	48	1.2	2
	126 to 135	52	1.3	2
	136 to 145	56	1.4	2
	146 to 155	60	1.5	2
	156 to 160	64	1.6	2

- Use Table 9 to determine total dose, injection volume, and number of vials required based on the patient's actual body weight for the 0.8 mg/kg dose using Talvey 40 mg/mL vial.

Table 9: 0.8 mg/kg Dose: Injection Volumes Using Talvey 40 mg/mL Vial

	Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial = 1.0 mL)
0.8 mg/kg Dose	35 to 39	29.6	0.74	1
	40 to 45	34	0.85	1
	46 to 55	40	1	1
	56 to 65	48	1.2	2
	66 to 75	56	1.4	2
	76 to 85	64	1.6	2
	86 to 95	72	1.8	2
	96 to 105	80	2	2
	106 to 115	88	2.2	3
	116 to 125	96	2.4	3
	126 to 135	104	2.6	3
	136 to 145	112	2.8	3
	146 to 155	120	3	3
	156 to 160	128	3.2	4

- Check that the Talvey solution for injection is colourless to light yellow. Do not use if the solution is discoloured, cloudy, or if foreign particles are present.
- Remove the appropriate strength Talvey vial(s) from refrigerated storage (2°C to 8°C) and equilibrate to ambient temperature (15°C to 30°C) for at least 15 minutes. Do not warm Talvey in any other way.
- Once equilibrated, gently swirl the vial for approximately 10 seconds to mix. Do not shake.
- Talvey is compatible with stainless steel injection needles and polypropylene or polycarbonate syringe material.
- Withdraw the required injection volume of Talvey from the vial(s) into an appropriately sized syringe using a transfer needle.
  - Each injection volume should not exceed 2.0 mL. Divide doses requiring greater than 2.0 mL equally into multiple syringes.
- Replace the transfer needle with an appropriately sized needle for injection.

Storage of prepared syringe

- The prepared syringes should be administered immediately. If immediate administration is not possible, store the Talvey solution for up to 24 hours refrigerated at 2°C to 8°C followed by up to 24 hours at ambient temperature of 15°C to 30°C. Discard if stored for more than 24 hours refrigerated or more than 24 hours of being at ambient temperature. If stored in the refrigerator, allow the solution to come to ambient temperature before administration.

Administration of Talvey

- Inject the required volume of Talvey into the subcutaneous tissue of the abdomen (preferred injection site). Alternatively, Talvey may be injected into the subcutaneous tissue at other sites (e.g., thigh). If multiple injections are required, Talvey injections should be at least 2 cm apart.
- Do not inject into tattoos or scars or areas where the skin is red, bruised, tender, hard or not intact.
- Any unused medicinal product or waste material should be disposed in accordance with local requirements.

4.5 Missed Dose

If a dose of Talvey is delayed, restart therapy based on recommendations in Table 10 and resume weekly or biweekly (every 2 weeks) dosing accordingly (see 4.2 Recommended Dose and Dosage Adjustment). Administer pretreatment medications prior to restarting Talvey, and monitor patients following administration of Talvey (see 4.4 Administration - Pretreatment medications).

Table 10: Recommendations for Restarting Talvey After Dose Delay

Dosing Schedule	Last Dose Administered	Time from Last Dose Administered	Talvey Recommendation[a]
Weekly Dosing Schedule	0.01 mg/kg	More than 7 days	Restart at 0.01 mg/kg
	0.06 mg/kg	8 to 28 days	Repeat 0.06 mg/kg
		More than 28 days	Restart at 0.01 mg/kg
	0.4 mg/kg	8 to 35 days	Repeat 0.4 mg/kg
		36 to 56 days	Restart at 0.06 mg/kg
		More than 56 days	Restart at 0.01 mg/kg
Biweekly (Every 2 Weeks) Dosing Schedule	0.01 mg/kg	More than 7 days	Restart at 0.01 mg/kg
	0.06 mg/kg	8 to 28 days	Repeat 0.06 mg/kg
		More than 28 days	Restart at 0.01 mg/kg
	0.4 mg/kg	8 to 35 days	Repeat 0.4 mg/kg
		36 to 56 days	Restart at 0.06 mg/kg
		More than 56 days	Restart at 0.01 mg/kg
	0.8 mg/kg	14 to 35 days	Repeat 0.8 mg/kg
		36 to 56 days	Restart at 0.4 mg/kg
		More than 56 days	Restart at 0.01 mg/kg

[a] Administer pretreatment medications prior to restarting Talvey. After restarting Talvey, resume weekly or biweekly (every 2 weeks) dosing accordingly (see 4.2 Recommended Dose and Dosage Adjustment).

5 OVERDOSAGE

Symptoms and signs

The maximum tolerated dose of talquetamab has not been determined. In clinical trials, doses of up to 1.2 mg/kg once every 2 weeks and 1.6 mg/kg monthly have been administered.

Treatment

In the event of an overdose, the patient should be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment should be instituted immediately.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, health professionals should record the brand name, the non-proprietary (active ingredient) name, and product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 11: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous injection	Solution for injection 3 mg/1.5 mL (2 mg/mL) strength: each 1.5 mL solution for injection contains 3 mg of talquetamab (2 mg of talquetamab per mL) 40 mg/1.0 mL (40 mg/mL) strength: each 1.0 mL solution for injection contains 40 mg of talquetamab (40 mg of talquetamab per mL)	EDTA disodium salt dihydrate Glacial acetic acid Polysorbate 20 Sodium acetate trihydrate Sucrose Water for injection

Talvey is a colourless to light yellow preservative-free solution for injection.

Talvey is available in a 1.5 mL vial (2 mg of talquetamab per mL) and a 1.0 mL vial (40 mg of talquetamab per mL).

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Driving and Operating Machinery

Due to the potential for ICANS, patients receiving Talvey are at risk of depressed level of consciousness (see 7 WARNINGS AND PRECAUTIONS). Advise patients to refrain from driving or operating heavy or potentially dangerous machinery during the step-up phase and for 48 hours after completion of the step-up phase (see 4.2 Recommended Dose and Dosage Adjustment) and in the event of new onset of any neurological symptoms, until symptoms

resolve.

Gastrointestinal

Oral toxicity

Oral toxicities, including dysgeusia, dry mouth, dysphagia, and stomatitis, occur very commonly while undergoing treatment with Talvey (see 8 ADVERSE REACTIONS and 16 NON-CLINICAL TOXICOLOGY).

Monitor patients for signs and symptoms of oral toxicity. Counsel patients to seek medical attention should signs or symptoms of oral toxicity occur and provide supportive care. Supportive care may include saliva stimulating agents, steroid mouth wash, or consultation with a nutritionist. Interrupt Talvey or consider less frequent dosing (see 4.2 Recommended Dose and Dosage Adjustment - Dose modifications for adverse reactions).

Over time, notable weight loss may occur (see 8 ADVERSE REACTIONS). Weight change should be monitored regularly during therapy. Clinically significant weight loss should be further evaluated. Talvey should be interrupted or less frequent dosing should be considered (see 4.2 Recommended Dose and Dosage Adjustment – Dose modifications for adverse reactions).

Hematologic

Cytopenias

Treatment-emergent Grade 3 or 4 neutropenia, febrile neutropenia and thrombocytopenia have been observed in patients who received Talvey (see 8 ADVERSE REACTIONS). A majority of events occurred during the first 8 to 10 weeks. Monitor complete blood counts during treatment and withhold Talvey as warranted. Provide supportive care according to current practice guidelines. Monitor patients with neutropenia for signs of infection (see 4.2 Recommended Dose and Dosage Adjustment - Dose modifications for adverse reactions).

Hypogammaglobulinaemia

Hypogammaglobulinaemia has been reported in patients receiving Talvey (see 8 ADVERSE REACTIONS). Immunoglobulin levels should be monitored during treatment with Talvey. Intravenous or subcutaneous immunoglobulin therapy was used to treat hypogammaglobulinemia. Patients should be treated according to local institutional guidelines, including infection precautions, antibiotic or antiviral prophylaxis, and administration of immunoglobulin replacement.

Immune

Cytokine release syndrome (CRS)

Cytokine release syndrome, including life-threatening or fatal reactions, have occurred in patients following treatment with Talvey (see 8 ADVERSE REACTIONS). Clinical signs and symptoms of CRS may include but are not limited to pyrexia, hypotension, chills, hypoxia, headache, and tachycardia. Potentially life-threatening complications of CRS may include

cardiac dysfunction, acute respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation (DIC).

Initiate Talvey therapy with step-up phase dosing and administer pre-treatment medications (corticosteroids, antihistamine, and antipyretics) prior to each dose of Talvey during the step-up phase to reduce the risk of CRS. Monitor patients following administration of Talvey accordingly. In patients who experience CRS, administer pre-treatment medications prior to the next Talvey dose (see 4.2 Recommended Dose and Dosage Adjustment and 4.4 Administration).

Counsel patients to seek medical attention should signs or symptoms of CRS occur. At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with supportive care, tocilizumab and/or corticosteroids, based on severity. The use of myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor (GM-CSF), should be avoided during CRS. Withhold Talvey until CRS resolves (see 4.2 Recommended Dose and Dosage Adjustment - Dose modifications for adverse reactions).

Serious infections

Serious infections, including life-threatening, opportunistic or fatal infections, have been reported in patients receiving Talvey (see 8 ADVERSE REACTIONS). Monitor patients for signs and symptoms of infection prior to and during treatment with Talvey and treat appropriately. Administer prophylactic antimicrobials according to local guidelines. Withhold Talvey as indicated (see 4.2 Recommended Dose and Dosage Adjustment - Dose modifications for adverse reactions).

New or reactivated viral infections occurred in clinical trials with Talvey. Before starting treatment with Talvey, screening for HBV infection, active HIV, and active HCV infection should be performed according to clinical guidelines. Due to the possibility of fulminant courses, patients with positive HBV serology should be monitored during treatment with Talvey and for at least six months after discontinuation for clinical symptoms and laboratory values that may be signs of HBV reactivation.

In patients who develop reactivation of HBV, have active HCV infection, or are known to be seropositive for HIV or acquired immune deficiency syndrome while on Talvey, treatment should be withheld as indicated in Table 5 and managed per local institutional guidelines (see 4.2 Recommended Dose and Dosage Adjustment - Dose modifications for adverse reactions).

Vaccines

Immune response to vaccines may be reduced when taking Talvey. The safety of immunization with live viral vaccines during or following Talvey treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 4 weeks prior to the start of treatment, during treatment, and at least 4 weeks after treatment.

Neurologic

Neurologic toxicities, including immune effector cell-associated neurotoxicity syndrome (ICANS)

Serious, life-threatening or fatal neurologic toxicities, including ICANS, have occurred following treatment with Talvey (see 8 ADVERSE REACTIONS*)*. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Clinical signs and symptoms of ICANS may include but are not limited to confusional state, depressed level of consciousness, disorientation, somnolence, lethargy, and bradyphrenia.

Monitor patients for signs and symptoms of neurologic toxicities and ICANS and treat promptly. Counsel patients to seek medical attention should signs or symptoms of neurologic toxicity and/or ICANS occur. At the first sign of neurologic toxicity and/or ICANS, immediately evaluate the patient and provide supportive care based on severity; withhold or discontinue Talvey based on severity and follow management recommendations (see 4.2 Recommended Dose and Dosage Adjustment - Dose modifications for adverse reactions).

Reproductive Health: Female and Male Potential

Fertility

There are no data on the effect of Talvey on fertility. Effects of Talvey on male and female fertility have not been evaluated in animal studies.

Skin

Skin reactions

Skin reactions including dry skin, exfoliation, rash, maculo-papular rash, erythema, erythematous rash, as well as nail disorders have occurred in patients who received Talvey (see 8 ADVERSE REACTIONS and 16 NON-CLINICAL TOXICOLOGY). Skin reactions including rash progression should be monitored for early intervention and treatment with corticosteroids. For Grade 3 or higher, or worsening Grade 1 or 2 rashes, oral steroids should also be administered. For non-rash skin reactions, dose modification may be considered (see Table 5). For skin reactions and nail disorders, Talvey should be withheld based on severity and institutional guidelines should be followed (see 4.2 Recommended Dose and Dosage Adjustment - Dose modifications for adverse reactions).

7.1 Special Populations

7.1.1 Pregnant Women

There are no available data on the use of Talvey in pregnant women or animal data to assess the risk of Talvey in pregnancy. Human IgG is known to cross the placenta after the first trimester of pregnancy. Therefore, talquetamab has the potential to be transmitted from the mother to the developing fetus. The effects of talquetamab on the developing fetus are unknown. Based on the mechanism of action, talquetamab may cause fetal harm when administered to a pregnant woman. Pregnant women should be advised there may be risks to the fetus.

Talvey is not recommended for women who are pregnant or for women of childbearing potential not using contraception.

Contraception

Advise females of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of Talvey.

Advise male patients with a female partner of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of Talvey.

7.1.2 Breast-feeding

It is not known whether talquetamab is excreted in human or animal milk, affects breastfed infants, or affects milk production. Because the potential for serious adverse reactions in breastfed infants is unknown for Talvey, advise patients not to breast-feed during treatment with Talvey and for at least 3 months after the last dose.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): Of the 339 patients treated with Talvey in MonumenTAL-1, 36% were 65 to less than 75 years of age, and 17% were 75 years of age or older. No clinically important differences in safety or effectiveness were observed in patients 65 to 75 years of age compared to younger patients. There are limited clinical data with talquetamab in patients 75 years of age or over. No dose adjustment is required (see 10.3 Pharmacokinetics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of Talvey was evaluated in 339 adult patients with relapsed or refractory multiple myeloma, including 51 patients exposed to prior T cell redirection therapy (i.e., chimeric antigen receptor (CAR)-T cells or bispecific T cell engaging monoclonal antibodies), who were treated with Talvey at the recommended dosing of 0.4 mg/kg weekly or 0.8 mg/kg once every 2 weeks. The median duration of treatment was 7.4 (range: 0.0 to 32.9) months.

The most frequent adverse reactions (≥ 20%) were CRS, dysgeusia, hypogammaglobulinemia, nail disorder, musculoskeletal pain, anemia, fatigue, skin disorder, weight decreased, rash, dry mouth, neutropenia, pyrexia, xerosis, thrombocytopenia, upper respiratory tract infection, lymphopenia, diarrhea, dysphagia, pruritus, cough, decreased appetite, pain, and headache. Serious adverse reactions reported in ≥ 2% of patients included CRS, pyrexia, sepsis, ICANS, COVID-19, viral infection, pneumonia, neutropenia, and pain. The most frequent adverse reactions leading to treatment discontinuation were ICANS (1.1%) and weight decreased

(0.9%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 12 summarizes adverse reactions reported in ≥10% of patients who received Talvey in MonumenTAL-1.

Table 12: Adverse Reactions (≥10%) in Patients With Multiple Myeloma Treated With Talvey in MonumenTAL-1 (N=339)

	Talvey N=339	
System Organ Class Adverse Reaction	**Any Grade n (%)**	**Grade 3 or 4 n (%)**
Blood and lymphatic system disorders		
Anemia[1]	158 (46.6%)	99 (29.2%)
Neutropenia[2]	120 (35.4%)	104 (30.7%)
Thrombocytopenia	101 (29.8%)	71 (20.9%)
Lymphopenia	91 (26.8%)	83 (24.5%)
Leukopenia	62 (18.3%)	38 (11.2%)
Gastrointestinal disorders		
Dysgeusia[3]	245 (72.3%)	0
Dry mouth	122 (36.0%)	0
Diarrhea	84 (24.8%)	4 (1.2%)
Dysphagia	82 (24.2%)	3 (0.9%)
Stomatitis[4]	67 (19.8%)	4 (1.2%)
Nausea	64 (18.9%)	0
Constipation	61 (18.0%)	0
Abdominal pain[5]	35 (10.3%)	1 (0.3%)
Vomiting	34 (10.0%)	2 (0.6%)
General disorders and administration site conditions		
Fatigue[6]	147 (43.4%)	12 (3.5%)
Pyrexia[7]	113 (33.3%)	6 (1.8%)
Pain[8]	76 (22.4%)	7 (2.1%)
Edema[9]	59 (17.4%)	0
Injection site reaction[10]	45 (13.3%)	0
Immune system disorders		
Cytokine release syndrome	260 (76.7%)	5 (1.5%)
Hypogammaglobulinaemia[11]	227 (67.0%)	0
Infections and infestations		
Upper respiratory tract infection[12]	98 (28.9%)	7 (2.1%)
COVID-19[a13]	63 (18.6%)	10 (2.9%)

System Organ Class Adverse Reaction	Talvey N=339 Any Grade n (%)	 Grade 3 or 4 n (%)
Fungal infection[14]	39 (11.5%)	1 (0.3%)
Bacterial infection[15]	38 (11.2%)	9 (2.7%)
Investigations		
Weight decreased	134 (39.5%)	11 (3.2%)
Transaminase elevation[16]	48 (14.2%)	12 (3.5%)
Metabolism and nutrition disorders		
Decreased appetite	76 (22.4%)	4 (1.2%)
Hypokalemia	55 (16.2%)	12 (3.5%)
Hypophosphatemia[17]	49 (14.5%)	21 (6.2%)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[18]	164 (48.4%)	12 (3.5%)
Nervous system disorders		
Headache[19]	69 (20.4%)	2 (0.6%)
Sensory neuropathy[20]	58 (17.1%)	0
Motor dysfunction[21]	45 (13.3%)	2 (0.6%)
Dizziness[22]	42 (12.4%)	8 (2.4%)
Encephalopathy[23]	38 (11.2%)	0
Respiratory, thoracic and mediastinal disorders		
Cough[24]	78 (23.0%)	0
Oral disorder[25]	46 (13.6%)	0
Dyspnea[a26]	39 (11.5%)	5 (1.5%)
Skin and subcutaneous tissue disorders		
Nail disorder[27]	191 (56.3%)	0
Skin disorder[28]	145 (42.8%)	0
Rash[29]	132 (38.9%)	12 (3.5%)
Xerosis[30]	109 (32.2%)	0
Pruritus	79 (23.3%)	1 (0.3%)

Adverse events are coded using MedDRA Version 25.0.

[a] Contains fatal outcome.

Note: The output includes the diagnosis of CRS; the symptoms of CRS are excluded.

Note: Per CTCAE v4.03, maximum toxicity grade for dysgeusia is 2 and maximum toxicity grade for dry mouth is 3.

1 Anemia: anemia, blood iron decreased and iron deficiency.

2 Neutropenia: febrile neutropenia and neutropenia.

3 Dysgeusia: ageusia, dysgeusia, hypogeusia and taste disorder.

4 Stomatitis: cheilitis, glossitis, glossodynia, mouth ulceration, oral discomfort, oral mucosal erythema, oral pain, stomatitis, swollen tongue, tongue discomfort, tongue erythema, tongue edema and tongue ulceration.

5 Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower and abdominal pain upper.

6 Fatigue: asthenia, fatigue, malaise and muscle fatigue.

7 Pyrexia: pyrexia and tumor associated fever.

8 Pain: burning feet syndrome, cancer pain, catheter site pain, coccydynia, ear pain, eye pain, flank pain, gastrointestinal pain, gingival pain, groin pain, lymph node pain, non-cardiac chest pain, pain, pain in jaw, pelvic pain, procedural pain, puncture site pain, sinus pain, tendon pain, testicular pain, toothache, tumor pain and urinary tract pain.

[9] Edema: face edema, fluid retention, gingival swelling, hypervolemia, joint swelling, lip swelling, edema, edema peripheral, periorbital edema, peripheral swelling and swelling.

[10] Injection site reaction: injection site discomfort, injection site erythema, injection site hemorrhage, injection site inflammation, injection site irritation, injection site plaque, injection site pruritus, injection site rash and injection site reaction.

[11] Hypogammaglobulinemia: hypogammaglobulinemia and/or subjects with laboratory IgG levels below 500 mg/dL following treatment with talquetamab.

[12] Upper respiratory tract infection: bronchiolitis, bronchitis, nasopharyngitis, pharyngitis, respiratory tract infection, respiratory tract infection bacterial, rhinitis, rhinovirus infection, sinusitis, tonsillitis, upper respiratory tract infection and viral upper respiratory tract infection.

[13] COVID-19: asymptomatic COVID-19, COVID-19, COVID-19 pneumonia, coronavirus infection and multisystem inflammatory syndrome.

[14] Fungal infection: body tinea, candida infection, ear infection fungal, fungal foot infection, fungal infection, fungal skin infection, genital candidiasis, esophageal candidiasis, onychomycosis, oral candidiasis, oral fungal infection, oropharyngeal candidiasis, tinea pedis, vulvovaginal candidiasis and vulvovaginal mycotic infection.

[15] Bacterial infection: campylobacter infection, carbuncle, cellulitis, citrobacter infection, clostridium difficile colitis, clostridium difficile infection, cystitis escherichia, cystitis klebsiella, diverticulitis, escherichia pyelonephritis, folliculitis, gastroenteritis escherichia coli, helicobacter gastritis, human ehrlichiosis, impetigo, moraxella infection, otitis media acute, pitted keratolysis, pyuria, relapsing fever, renal abscess, skin infection, staphylococcal infection, tooth abscess, tooth infection, urinary tract infection enterococcal and urinary tract infection pseudomonal.

[16] Transaminase elevation includes: alanine aminotransferase increased and aspartate aminotransferase increased.

[17] Hypophosphatemia: blood phosphorus decreased and hypophosphatemia.

[18] Musculoskeletal pain: arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, osteoarthritis, pain in extremity and sacral pain.

[19] Headache: headache, migraine, procedural headache, and tension headache.

[20] Sensory neuropathy: dysesthesia, hyperesthesia, hypoesthesia, hypoesthesia oral, immune-mediated neuropathy, neuralgia, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, polyneuropathy, sciatica and vestibular neuronitis.

[21] Motor dysfunction: dysarthria, dysgraphia, dysmetria, dysphonia, gait disturbance, muscle atrophy, muscle spasms, muscular weakness, peripheral motor neuropathy and tremor.

[22] Dizziness: dizziness, syncope and vertigo.

[23] Encephalopathy: agitation, amnesia, aphasia, bradyphrenia, confusional state, delirium, disorientation, disturbance in attention, encephalopathy, hallucination, lethargy, memory impairment, mood altered, restlessness, sleep disorder and somnolence.

[24] Cough: cough, productive cough, and upper-airway cough syndrome.

[25] Oral disorder: oral disorder, oral dysesthesia, oral mucosal exfoliation, oral toxicity and oropharyngeal pain.

[26] Dyspnea: acute respiratory failure, dyspnea, dyspnea exertional, respiratory failure, and tachypnea.

[27] Nail disorder: koilonychia, nail bed disorder, nail cuticle fissure, nail discolouration, nail disorder, nail dystrophy, nail hypertrophy, nail pitting, nail ridging, nail toxicity, onychoclasis, onycholysis and onychomadesis.

[28] Skin disorder: palmar-plantar erythrodysesthesia syndrome, palmoplantar keratoderma, skin discolouration, skin exfoliation and skin fissures.

[29] Rash: dermatitis, dermatitis acneiform, dermatitis contact, dermatitis exfoliative, dermatitis exfoliative generalized, erythema, exfoliative rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular and stasis dermatitis.

[30] Xerosis: dry eye, dry skin and xerosis.

Description of Selected Adverse Reactions

Cytokine release syndrome

In MonumenTAL-1 (N=339), CRS occurred in 77% of patients. Most events were Grade 1 or 2, with Grade 3 events occurring in 1.5% of patients. Thirty-one percent (31%) of patients experienced more than one CRS event. Most events occurred during the first (29%), or second (44%) step-up dose. In the biweekly regimen, 33% of patients had CRS after the third step-up dose. CRS occurred in 30% of patients with the first 0.4 mg/kg treatment dose and in 12% of patients treated with the first 0.8 mg/kg treatment dose. CRS was observed in less than 3% of patients during the remaining doses in cycle 1 and in less than 4% of patients from week 5 onward. After week 5, all instances of CRS were Grade 1. The median time to onset of CRS was 27 (range: 0.1 to 333) hours from the last dose, 91% of events occurred within 48 hours from the last dose, and the median duration was 17 (range: 0 to 622) hours. Tocilizumab and corticosteroids were used to treat 39% and 5% of CRS events, respectively.

Neurologic toxicities, including immune effector cell-associated neurotoxicity syndrome (ICANS)

In MonumenTAL-1, neurologic toxicities were reported in 29% (n=98) of 339 patients receiving Talvey at the recommended dosages. Neurologic toxicity events were Grade 1 (17%), Grade 2 (10%), Grade 3 (2.4%) or Grade 4 (0.3%). The most frequently reported neurologic toxicity event was headache (9%).

In MonumenTAL-1, ICANS occurred in 10% (n=26) of 265 patients who received Talvey at the recommended dosages and for whom ICANS data was collected. Most events were Grade 1 or 2, with Grade 3 and 4 events occurring in 2.3% of patients. The most frequently reported clinical manifestations of ICANS were confusional state (4.2%), disorientation (1.9%), and somnolence (1.9%). Sixty-eight percent (68%) of patients with ICANS had concurrent CRS (during or within 7 days of CRS resolution). Three percent (3%) of patients experienced more than one ICANS event. Most ICANS occurred during the step-up phase following the first or second dose, or the initial treatment dose (0.4 mg/kg and 0.8 mg/kg) (3% each). The median time to onset was 28 (range: 3 to 355) hours from the last dose, 68% of events started within 48 hours from the last dose, and the median duration was 9 (range: 2 to 194) hours.

One fatal ICANS event was reported in MonumenTAL-1.

Serious infections

In MonumenTAL-1 (N=339), Grade 3 or Grade 4 infections occurred in 19% of patients, and fatal infections occurred in 1.5% of patients.

Skin reactions

In MonumenTAL-1 (N=339), 31% of patients experienced rashes that were Grade 1 or 2, with Grade 3 events occurring in 3.5% of patients. The median time to onset for rash was 22 days.

Immunogenicity

In MonumenTAL-1, 260 patients treated with subcutaneous talquetamab monotherapy at 0.4

mg/kg weekly or 0.8 mg/kg biweekly (every 2 weeks) were evaluated for antibodies to talquetamab. Following treatment of 0.4 mg/kg weekly or 0.8 mg/kg biweekly (every 2 weeks), 64 of 260 patients (24.6%) developed anti-talquetamab antibodies. None of these participants were positive for neutralizing antibodies to talquetamab.

8.3 Less Common Clinical Trial Adverse Reactions

Clinically relevant adverse reactions reported in <10% of patients who received Talvey in MonumenTAL-1 included:

- ICANS (9.8%)
- Viral infection (8.3%; includes adenovirus infection, conjunctivitis viral, cytomegalovirus infection, cytomegalovirus viraemia, disseminated varicella zoster virus infection, gastroenteritis rotavirus, gastroenteritis viral, HCoV-HKU1 infection, herpes ophthalmic, influenza, metapneumovirus infection, norovirus infection, parainfluenzae virus infection, respiratory syncytial virus bronchiolitis, respiratory syncytial virus infection, retinitis viral and viral infection)
- Pneumonia (6.8%; includes pneumonia and pneumonia streptococcal)
- Sepsis[a] (5.0%; includes bacteremia, enterobacter bacteremia, escherichia sepsis, fungal sepsis, klebsiella bacteraemia, klebsiella sepsis, pneumococcal sepsis, pseudomonal bacteraemia, salmonella sepsis, sepsis, septic shock, staphylococcal bacteremia, staphylococcal sepsis and streptococcal bacteremia)

[a] Contains fatal outcome.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 13 summarizes clinical laboratory measurements that worsened from baseline in ≥30% of patients who received Talvey in MonumenTAL-1.

Table 13: Laboratory Abnormalities (≥30%) That Worsened From Baseline in Patients With Multiple Myeloma Who Received Talvey in MonumenTAL-1

	Talvey (N=339)	
Laboratory Abnormality	**Any Grade (%)**	**Grade 3 or 4 (%)**
Hematology		
Lymphocyte count decreased	90.0	79.4
White blood cell decreased	76.1	36.3
Hemoglobin decreased	69.0	31.6
Neutrophil count decreased	68.1	35.4
Platelet count decreased	62.8	22.7
Chemistry		
Albumin decreased	65.2	2.1
Alkaline phosphatase increased	51.6	1.5
Phosphate decreased	45.7	13.3
Gamma-glutamyl transferase increased	39.5	7.4

Laboratory Abnormality	Talvey (N=339)	
	Any Grade (%)	Grade 3 or 4 (%)
Alanine Aminotransferase increased	36.6	3.2
Aspartate aminotransferase increased	35.7	3.5
Potassium decreased	33.3	5.3
Sodium decreased	32.2	5.9

Laboratory toxicity grades are derived based on the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No drug interaction studies have been performed with Talvey.

9.4 Drug-Drug Interactions

Talquetamab causes release of cytokines (see 10.2 Pharmacodynamics) that may suppress the activity of cytochrome P450 (CYP) enzymes, potentially resulting in increased exposure to CYP substrates. Based on simulations from a semi-mechanistic PK model, the highest risk of drug-drug interaction is expected to occur beginning at the initiation of the talquetamab step-up phase ending approximately 9 days after the first treatment dose and during and after CRS (see 7 WARNINGS AND PRECAUTIONS - CRS). Monitor for toxicity and monitor the concentrations of drugs that are CYP (e.g., CYP2C9, CYP2C19, CYP3A4/5) substrates where minimal concentration changes may lead to serious adverse reactions. Adjust the dose of the concomitant CYP (e.g., CYP2C9, CYP2C19, CYP3A4/5) substrate drugs as needed.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Talquetamab is a humanized immunoglobulin G4 proline, alanine, alanine (IgG4 PAA) bispecific antibody directed against GPRC5D on multiple myeloma cells and the CD3 receptor on T cells. Talquetamab promotes enhanced T cell-mediated cytotoxicity through recruitment of CD3-expressing T cells to GPRC5D-expressing cells. This leads to the activation of T cells and induces

subsequent lysis of GPRC5D-expressing cells mediated by secreted perforin and various granzymes stored in the secretory vesicles of cytotoxic T cells. Based on the expression of GPRC5D on plasma cells with minimal to no expression detected on B cells and B cell precursors, talquetamab targets multiple myeloma cells particularly. GPRC5D protein is also expressed in healthy tissues such as epithelial cells in keratinized tissues of the skin and tongue.

10.2 Pharmacodynamics

Within the first month of treatment with talquetamab, activation and redistribution of T cells and induction of serum cytokines were observed.

10.3 Pharmacokinetics

0.4 mg/kg Weekly

The mean accumulation ratio between the doses on day 1 and day 43 of talquetamab 0.4 mg/kg was 3.94 ± 2.79 (n=13) and 4.50 ± 3.85 (n=13) for C_{max} and AUC_{tau}, respectively.

Pharmacokinetic parameters of talquetamab following the 1st and 7th recommended weekly dose of 0.4 mg/kg are shown in Table 14.

Table 14: Estimation of Pharmacokinetic Parameters of Talquetamab by Non-Compartmental Analysis Following the First and Seventh Recommended 0.4 mg/kg Weekly SC Dose in Patients With Relapsed or Refractory Multiple Myeloma in MonumenTAL-1 (Step-up Dose 0.01/0.06 Then 0.4 mg/kg).

Pharmacokinetic Parameters	1st dose of 0.4 mg/kg	7th dose on day 43 of 0.4 mg/kg
T_{max} (days)	2.93 (0.98 - 7.75) (n=21)	2.01 (0.94 - 5.97) (n=13)
C_{max} (ng/mL)	1,568 ± 1,185 (n=21)	3,799 ± 2,411 (n=13)
C_{trough} (ng/mL)	178 ± 124 (n=19)	2,548 ± 1,308 (n=13)
AUC_{tau} (ng·h/mL)	178,101 ± 130,802 (n=17)	607,297 ± 371,399 (n=10)
CL/F (L/h)	NR	0.0773 ± 0.0409 (n=10)
V_d/F (L)	NR	9.34 (n=1)

T_{max} = Time to reach the C_{max}; C_{max} = Maximum observed serum talquetamab concentration; C_{trough} = Observed serum talquetamab concentration prior to next dose; AUC_{tau} = Area under the concentration-time curve over the weekly dosing interval; CL/F = Total apparent clearance of drug after extravascular administration; V_d/F = Apparent volume of distribution after extravascular administration; NR = Not reportable. Data are presented as mean ± standard deviation, except for T_{max} which is presented as median (minimum-maximum).

0.8 mg/kg Biweekly (Every Two Weeks)

The mean accumulation ratio between the doses on day 1 and day 57 of talquetamab 0.8 mg/kg was 2.33 ± 1.79 (n=19) and 2.17 ± 1.78 (n=19) for C_{max} and AUC_{tau}, respectively.

Pharmacokinetic parameters of talquetamab following the 1st and 5th recommended biweekly (every 2 weeks) dose of 0.8 mg/kg are shown in Table 15.

Table 15: Estimation of Pharmacokinetic Parameters of Talquetamab by Non-Compartmental Analysis Following the First and Fifth Recommended 0.8 mg/kg Biweekly (Every 2 Weeks) SC Dose in Patients With Relapsed or Refractory Multiple Myeloma in MonumenTAL-1 (Step-up Dose 0.01/0.06/0.3 Then 0.8 mg/kg).

Pharmacokinetic Parameters	1st dose of 0.8 mg/kg	5th dose on day 57 of 0.8 mg/kg
T_{max} (days)	2.83 (1.68 - 13.98) (n=33)	2.85 (0.96 - 7.82) (n=19)
C_{max} (ng/mL)	2,507 ± 1,568 (n=33)	4,161 ± 2,021 (n=19)
C_{trough} (ng/mL)	597 ± 437 (n=32)	1,831 ± 841 (n=17)
AUC_{tau} (ng·h/mL)	675,764 ± 399,680 (n=28)	1,021,059 ± 383,417 (n=17)
CL/F (L/h)	NR	0.0641 ± 0.0341 (n=17)
V_d/F (L)	NR	288 (n=1)

T_{max} = Time to reach the C_{max}; C_{max} = Maximum observed serum talquetamab concentration; C_{trough} = Observed serum talquetamab concentration prior to next dose; AUC_{tau} = Area under the concentration-time curve over the Q2W dosing interval; CL/F = Total apparent clearance of drug after extravascular administration; V_d/F = Apparent volume of distribution after extravascular administration; NR = Not reportable. Data are presented as mean ± standard deviation, except for T_{max} which is presented as median (minimum-maximum).

Absorption

Based on the population pharmacokinetic model, the typical value of the bioavailability of talquetamab was 62% when administered subcutaneously relative to intravenous dosing. The rate of absorption from the SC administration was 0.138 day^{-1}.

Distribution

Based on the population pharmacokinetic model, the typical value of the volume of distribution was 4.3 L (22% CV [coefficient of variation]) for the central compartment, and 5.8 L (83% CV) for the peripheral compartment.

Elimination

The population pharmacokinetic model for talquetamab incorporated both linear time-independent and time-dependent clearance parameters. Based on the population pharmacokinetic model, the typical total clearance parameter is 2.08 ± 1.08 L/day at initial treatment and 1.06 ± 0.548 L/day at steady state for participants with IgG subtype of myeloma and ISS stage I. The time-dependent component of the clearance parameter accounted for 48.8% of total clearance estimate at initial treatment and then decreased exponentially to <5% at around Week 16.

Based on the population pharmacokinetic model, the concentration-time profile at Week 16 would reach 90% of steady-state concentration for both 0.4 mg/kg weekly and 0.8 mg/kg

biweekly regimens. The median terminal phase half-life based on the post hoc parameters of all SC population (N=392) was 7.56 days at initial treatment, and 12.2 days at steady state.

An alternative estimate of the half-life, based on the observed data, was provided by the non-compartmental analysis of the IV population (n=86) which estimated the half-life as 3.51 ± 2.07 days.

Special Populations and Conditions

- **Pediatrics:** The pharmacokinetics of talquetamab in pediatric patients <18 years of age have not been investigated.
- **Geriatrics:** Results of population pharmacokinetic analyses indicate that age (33 to 86 years) likely did not influence the pharmacokinetic parameters in the population pharmacokinetic model of talquetamab.
- **Hepatic Insufficiency:** No formal studies of talquetamab in patients with hepatic impairment have been conducted.

  Results of population pharmacokinetic analyses indicate that mild hepatic impairment (total bilirubin >1 to 1.5 times upper limit of normal [ULN] and any aspartate aminotransferase [AST], or total bilirubin ≤ULN and AST>ULN) and moderate hepatic impairment (total bilirubin 1.5 to 3 times ULN and any AST>ULN) did not significantly influence the pharmacokinetics of talquetamab. No data is available in patients with severe hepatic impairment.
- **Renal Insufficiency:** No formal studies of talquetamab in patients with renal impairment have been conducted.

  Results of population pharmacokinetic analyses indicate that mild (60 mL/min/1.73 m^2 ≤ estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2) or moderate (30 mL/min/1.73 m^2 ≤ eGFR <60 mL/min/1.73 m^2) renal impairment did not significantly influence the pharmacokinetics of talquetamab. No data is available in patients with severe renal impairment.

11 STORAGE, STABILITY AND DISPOSAL

Store refrigerated at 2°C to 8°C. Do not freeze.

Store in the original carton in order to protect from light.

Keep out of the sight and reach of children.

Prepared syringe:

The prepared syringes should be administered immediately. If immediate administration is not possible, store the Talvey solution for up to 24 hours refrigerated at 2°C to 8°C followed by up to 24 hours at ambient temperature of 15°C to 30°C. Discard if stored for more than 24 hours refrigerated or more than 24 hours of being at ambient temperature. If stored in the refrigerator, allow the solution to come to ambient temperature before administration.

12 SPECIAL HANDLING INSTRUCTIONS

Any unused medicinal product or waste material should be disposed in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: talquetamab

Molecular formula and molecular mass: approximately 147 kDa

Structure: Talvey (talquetamab) is a humanized immunoglobulin G4-proline, alanine, alanine (IgG4-PAA)-based bispecific antibody directed against G Protein-coupled receptor family C group 5 member D (GPRC5D) and the cluster of differentiation 3 (CD3) receptors.

Physicochemical properties: Talvey is a colourless to light yellow preservative-free solution for injection.

Product Characteristics:

Talvey is produced by cultivation of recombinant Chinese hamster ovary cells, followed by isolation, chromatographic purification, and formulation.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Monotherapy for Multiple Myeloma After Three or More Prior Lines of Therapy

The clinical efficacy of Talvey monotherapy was evaluated in adult patients with relapsed or refractory multiple myeloma in an open-label, non-randomized, multicenter, Phase I/II study (MonumenTAL-1). See Table 16 for a summary of study design and dosing.

Table 16: Summary of Patient Demographics for Clinical Trials in Adult Patients With Relapsed or Refractory Multiple Myeloma Who Have Received at Least Three Prior Lines of Therapy, Including a Proteasome Inhibitor, an Immunomodulatory Agent and an Anti-CD38 Monoclonal Antibody

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
MMY1001 (MonumenTAL-1)	Phase 1/2, single-arm, open-label, multicenter study to evaluate the safety and efficacy of Talvey in adult patients with relapsed or refractory multiple myeloma who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.	Talvey 0.4 mg/kg subcutaneously weekly, following two step-up doses (0.01 and 0.06 mg/kg) in the first week of therapy, until disease progression or unacceptable toxicity.	n = 143	67 years (range: 46 to 86 years)	54.5% male, 45.5% female
		Talvey 0.8 mg/kg subcutaneously biweekly (every 2 weeks), following three step-up doses (0.01, 0.06 and 0.3 mg/kg) until disease progression or unacceptable toxicity.	n = 145	67 years (range: 38 to 84 years)	57.2% male, 42.8% female

Study MonumenTAL-1 enrolled patients with relapsed or refractory multiple myeloma. Patients in Phase 1 had progressed on, or could not tolerate, all previous lines of therapy. Patients in Phase 2 had received at least three prior lines of therapy and must have previously received a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. All patients in the pivotal cohorts were naïve to T cell redirecting therapies such as chimeric antigen receptor-T cells or other bispecific monoclonal antibodies.

The study included adults with measurable multiple myeloma who had an Eastern Cooperative Oncology Group (ECOG) score of ≤ 2, adequate baseline laboratory values (absolute neutrophil count ≥ 1.0 x 10^9/L, platelet count ≥ 50 x 10^9/L, hemoglobin level ≥ 8 g/dL) and renal (CrCL ≥ 40 mL/min), and hepatic (AST and ALT ≤ 3.0 x ULN, total bilirubin ≤ 2.0 x ULN) function. The study excluded patients who: received T cell redirection therapy in the preceding 3 months; had prior Grade 3 or higher CRS related to any T cell redirection therapy; allogenic stem cell transplant in the preceding 6 months; autologous stem cell transplant in the preceding 3

months; stroke or seizure within the past 6 months; CNS involvement or clinical signs of meningeal involvement of multiple myeloma; plasma cell leukaemia; POEMS syndrome; primary light chain amyloidosis; active or documented history of autoimmune disease, with the exception of vitiligo, resolved childhood atopic dermatitis, and prior Grave's disease that was euthyroid based on clinical symptoms and laboratory testing.

Patients received Talvey 0.4 mg/kg subcutaneously weekly, following two step-up doses (0.01 and 0.06 mg/kg) in the first week of therapy, or Talvey 0.8 mg/kg subcutaneously biweekly (once every 2 weeks), following three step-up doses (0.01, 0.06 and 0.3 mg/kg), until disease progression or unacceptable toxicity. Patients were hospitalized for monitoring for at least 48 hours after each Talvey dose during the step-up phase.

Of 143 patients treated with Talvey 0.4 mg/kg weekly, the median age was 67 (range: 46 to 86) years, 55% were male, 90% were White, and 8% were Black or African American. Patients had received a median of 5 (range: 2 to 13) prior therapies, and 78% of patients had received prior autologous stem cell transplantation (ASCT). Ninety-four percent (94%) of patients were refractory to their last therapy and 74% were refractory to a proteasome inhibitor, immunomodulatory agent, and anti-CD38 antibody. Of the 132 patients for whom baseline cytogenetic data were available, high-risk cytogenetic factors (presence of t(4:14), t(14:16), and/or del(17p)) were present in 31% of patients.

Of 145 patients treated with Talvey 0.8 mg/kg biweekly (every 2 weeks), the median age was 67 (range: 38 to 84) years, 57% were male, 86% were White, and 6% were Black or African American. Patients had received a median of 5 (range: 2 to 17) prior therapies, and 79% of patients had received prior autologous stem cell transplantation (ASCT). Ninety-four percent (94%) of patients were refractory to their last therapy and 69% were refractory to a proteasome inhibitor, immunomodulatory agent, and anti-CD38 antibody. Of the 128 patients for whom baseline cytogenetic data were available, high-risk cytogenetic factors (presence of t(4:14), t(14:16), and/or del(17p)) were present in 29% of patients.

The primary efficacy outcome of MonumenTAL-1 was the overall response rate (ORR) as assessed by an Independent Review Committee (IRC) applying International Myeloma Working Group (IMWG) criteria (See Table 17 and Table 18).

The median duration of follow-up among all patients receiving Talvey 0.4 mg/kg weekly was 18.8 months. The median time to response was 1.2 months (range: 0.2, 10.9) and the median time to best response was 2.2 months (range: 0.8, 12.7).

Table 17: Efficacy Results for MonumenTAL-1 (Study MMY1001) in Patients Receiving 0.4 mg/kg Weekly Talvey

	0.4 mg/kg Weekly (N=143)
Overall response rate (ORR=sCR+CR+VGPR+PR)	106 (74.1%)
95% CI (%)	(66.1, 81.1)
Stringent complete response (sCR)	34 (23.8%)
Complete response (CR)	14 (9.8%)
Very good partial response (VGPR)	37 (25.9%)

Partial response (PR)	21 (14.7%)
Duration of Response (DOR)	
Number of responders	106
Median DOR[a] (95% CI) (months)	9.5 (6.7, 13.3)
Patients with DOR ≥ 6 months[a] (95% CI)	67.2% (57.2, 75.3)
Patients with DOR ≥ 12 months[a] (95% CI)	43.5% (33.8, 52.8)

CI=confidence interval

[a] Kaplan-Meier estimate

The median duration of follow-up among all patients receiving Talvey 0.8 mg/kg once every 2 weeks was 12.7 months. The median time to response was 1.3 months (range: 0.2, 9.2) and the median time to best response was 3.0 months (range: 0.3, 12.9).

Table 18: Efficacy Results for MonumenTAL-1 (Study MMY1001) in Patients Receiving 0.8 mg/kg Biweekly (Every 2 Weeks) Talvey

	0.8 mg/kg Biweekly (Every 2 Weeks) (N=145)
Overall response rate (ORR=sCR+CR+VGPR+PR)	104 (71.7%)
95% CI (%)	(63.7, 78.9)
Stringent complete response (sCR)	43 (29.7%)
Complete response (CR)	13 (9.0%)
Very good partial response (VGPR)	32 (22.1%)
Partial response (PR)	16 (11.0%)
Duration of Response (DOR)	
Number of responders	104
Median DOR[a] (95% CI) (months)	NE (13.0, NE)
Patients with DOR ≥ 6 months [a] (95% CI)	82.2% (73.2, 88.4)
Patients with DOR ≥ 9 months [a] (95% CI)	76.3% (66.5, 83.7)

CI=confidence interval; NE=not estimable

[a] Kaplan-Meier estimate

ORR results were consistent across pre-specified subgroups, including number of prior lines of therapy, refractoriness to prior therapy, and cytogenetic risk at baseline.

The ORR was generally consistent in a separate cohort of MonumenTAL-1, which included a limited number of patients (n=51) who were exposed to prior T cell redirection therapy and had received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Tissue Profiling: Normal (non-diseased) human tissue expression studies were conducted to detect GPRC5D mRNA by in situ hybridization and protein by immunohistochemistry. In human skin, GPRC5D is expressed in epithelial cells of hair follicles and eccrine sweat glands.

Consistent with this pattern of expression, clinical adverse events including skin exfoliation, dry skin and nail disorder have been reported following administration of Talvey.

GPRC5D was also shown in non-clinical studies to be expressed in filiform papillae of the tongue and in plasma cells of the oral cavity. On-target off-tumour binding of GPRC5D by talquetamab at these sites is consistent with the oral toxicities associated with this bispecific antibody.

Carcinogenicity: No animal studies have been performed to assess the carcinogenic potential of talquetamab.

Genotoxicity: No animal studies have been performed to assess the genotoxic potential of talquetamab.

Reproductive and Developmental Toxicology: No animal studies have been conducted to evaluate the effects of talquetamab on reproduction and fetal development.

No studies have been conducted to evaluate the effects of talquetamab on fertility.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

TALVEY™

(talquetamab injection)

Read this carefully before you receive **Talvey (Tal' vay)**. This is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Talvey**.

Serious Warnings and Precautions

- Fever and chills which may be symptoms of a serious side effect called cytokine release syndrome (CRS), which can be severe or fatal. Other symptoms of CRS may include difficulty in breathing, dizziness or feeling light-headed, feeling the need to throw up, headache, fast heartbeat, low blood pressure, feeling tired, vomiting, muscle pain and joint pain.
- Neurologic problems which may include symptoms like headache, confusion, difficulty with memory, difficulty speaking or slow speech, difficulty understanding speech, difficulty in writing, confused about time or surroundings, being less alert, or excessive sleepiness, and seizures (fits) which can be serious or life-threatening. Some of these may be signs of a serious immune reaction called 'immune effector cell associated neurotoxicity syndrome' (ICANS). These effects can occur days or weeks after you receive the injection, and may initially be subtle.
- Your healthcare provider will monitor for signs and symptoms of CRS and neurological problems during treatment with Talvey. You should call your healthcare provider right away if you develop any of the signs and symptoms of CRS or neurologic problems at any time during your treatment with Talvey.

What is Talvey used for?

Talvey is used to treat patients with a type of cancer of the bone marrow called multiple myeloma. It is given when your cancer has not responded to or has come back after at least three different treatments, and your cancer is not responding to your most recent therapy. Talvey is given alone to treat multiple myeloma.

For the following indication Talvey has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

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

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does Talvey work?

Talvey is a cancer medicine that contains the active substance 'talquetamab'.

Talvey is an antibody, which is a type of protein. It has been designed to recognise and attach to specific targets in your body.

Talvey targets proteins found on cells in the blood:

- GPRC5D (G Protein-coupled receptor family C group 5 member D), found on multiple myeloma cancer cells, and
- CD3 (cluster of differentiation 3), found in your immune system.

This medicine works by attaching to these cells so that your immune system can destroy the multiple myeloma cancer cells.

What are the ingredients in Talvey?

Medicinal ingredients: talquetamab

Non-medicinal ingredients: EDTA disodium salt dihydrate, glacial acetic acid, polysorbate 20, sodium acetate trihydrate, sucrose, and water for injection.

Talvey comes in the following dosage forms:

Talvey comes in 2 different strengths:

- Talquetamab 3 mg/1.5 mL (2 mg/mL)
- Talquetamab 40 mg/1.0 mL (40 mg/mL)

Talvey is a solution for injection and is a colourless to light yellow liquid. Talvey is supplied as a carton pack containing 1 glass vial.

Do not use Talvey if:

If you are allergic to talquetamab or any of the other ingredients of this medicine (listed in "What are the ingredients in Talvey?"). If you are not sure, talk to your healthcare professional before you receive Talvey.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive Talvey. Talk about any health conditions or problems you may have, including if you:

- Have an infection, or had an infection with hepatitis virus in the past. An infection will be treated before you receive Talvey.
- Have had a stroke or seizure, or any other types of neurological problems within the past 6 months.
- Have had a recent vaccination or are going to have a vaccination. You should not receive live vaccines four weeks before, during, or four weeks after your final dose of Talvey.
- Are pregnant, think you might be pregnant, or plan to become pregnant. If you or your partner could become pregnant, you must use effective contraception during treatment and for 3 months after stopping treatment with Talvey. If you or your partner become pregnant while being treated with this medicine, tell your healthcare professional right away.
- Are breast-feeding or plan to breast-feed. It is not known if Talvey passes into breast milk. Ask your healthcare professional for advice before receiving this medicine. You and your healthcare professional will decide if the benefit of breast-feeding is greater than the risk to your baby.

Other warnings you should know about:

Driving and using machines:

- Some people may feel tired, dizzy, or confused while taking Talvey. Do not drive, use tools, or operate heavy machinery or do things that could pose a danger to you or others in the 48 hours after receiving your first three (0.4 mg/kg dosing schedule) or four (0.8 mg/kg dosing schedule) doses of Talvey, or until instructed by your healthcare professional.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Interactions with other drugs, vitamins, minerals, natural supplements or alternative medicines have not been established with Talvey.

How you will receive Talvey:

Talvey will be given to you by a healthcare professional in a healthcare setting. Talvey will be given to you by a healthcare professional as an injection under your skin ('subcutaneous' injection). It is given in the stomach area (abdomen) or thigh.

Before you receive Talvey your healthcare professional will check:

- Your blood counts
- For signs of infection - an infection will be treated before you have Talvey
- If you are pregnant or breast-feeding

Medicines given during treatment with Talvey

Before the first three doses of the 0.4 mg/kg dosing schedule or the first four doses of the 0.8 mg/kg dosing schedule of Talvey, you will be given medicines which help to lower the chance of side effects. These may include:

- Medicines for an allergic reaction (antihistamines)
- Medicines for inflammation (corticosteroids)
- Medicines for fever (such as paracetamol)

You may be given these medicines for later doses of Talvey based on any symptoms you have.

You may also be given additional medicines based on any symptoms you experience or your medical history.

After you receive Talvey your healthcare professional will:

- Monitor you for side effects
- Regularly check your blood counts, as the number of blood cells and other blood components may decrease

Usual dose:

Your healthcare professional will determine your dose of Talvey. The dose of Talvey will depend on your body weight.

Talvey is given either once a week or once every 2 weeks as follows:

<u>0.4 mg/kg once a week:</u>

- You will receive 0.01 mg for each kilogram of bodyweight for your first dose.
- You will receive 0.06 mg per kilogram of bodyweight as your second dose 2-4 days later.
- You will then receive a 'Treatment dose' of 0.4 mg per kilogram of bodyweight 2-4 days after your second dose.
- You will then continue receiving a 'Treatment dose' once a week.
- Treatment will continue for as long as you are getting benefit from Talvey.

Your healthcare professional will monitor you for side effects for 2 days after each of your first three doses. You should stay close to a healthcare facility after each of the first three doses in case you have side effects. Your healthcare professional may decide to hospitalize you after each of the first three doses. Your healthcare professional will tell you if you need to be monitored after other doses.

0.8 mg/kg once every 2 weeks:

- You will receive 0.01 mg for each kilogram of bodyweight for your first dose.
- You will receive 0.06 mg per kilogram of bodyweight as your second dose 2-4 days later.
- You will receive 0.4 mg per kilogram of bodyweight as your third dose 2-4 days later.
- You will then receive a 'Treatment dose' of 0.8 mg per kilogram of bodyweight 2-4 days after your third dose.
- You will then continue receiving a 'Treatment dose' once every 2 weeks.
- Treatment will continue for as long as you are getting benefit from Talvey.

Your healthcare professional will monitor you for side effects for 2 days after each of your first four doses. You should stay close to a healthcare facility after each of the first four doses in case you have side effects. Your healthcare professional may decide to hospitalize you after each of the first four doses. Your healthcare professional will tell you if you need to be monitored after other doses.

Overdose:

Talvey will be given by your healthcare professional. In the event that you receive too much (an overdose), your healthcare professional will check you for side effects.

If you think you, or a person you are caring for, have received too much Talvey, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

It is very important to go to all your appointments to make sure your treatment works. If you miss an appointment, make another one as soon as possible.

What are possible side effects from using Talvey?

Like all medicines, this medicine can cause side effects, although not everybody gets them. These are not all the possible side effects you may have when taking Talvey. If you experience any side effects not listed here, tell your healthcare professional.

Very common (may affect more than 1 in 10 people):

- low level of antibodies called 'immunoglobulins' in the blood, which may make infections more likely

- Nail problems
- Muscle and joint pain
- Low number of red blood cells
- Feeling very tired
- Weight loss
- Low number of a type of white blood cells (lymphocytes)
- Diarrhoea, nausea, or constipation
- Infected nose, sinuses or throat (cold)
- Itching
- Decreased appetite
- Abnormally dry skin that may affect the protective linings of the body (such as the mouth and eyes)
- Pain
- Low number of white blood cells
- Low level of 'potassium' or 'phosphate' in the blood
- Swelling caused by fluid build up in the body
- Irritation or pain where the injection is given
- Increased level of 'transaminases' in the blood
- COVID-19 infection caused by a virus called coronavirus (SARS-CoV-2)
- Bacterial infection
- Problems with the mouth
- Fungal infection
- Nerve damage that may cause tingling, numbness, pain, or loss of pain sensation
- Problems being able to produce or control movement
- Feeling dizzy
- Change in brain function (encephalopathy)
- Abdominal pain
- Vomiting

Common (may affect up to 1 in 10 people):

- Viral infection
- Pneumonia (lung infection)
- Severe infection throughout the body (sepsis)

Get medical help straight away if you get any of the following serious side effects which may be severe and can be fatal.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON (may affect more than 1 in 10 people)			
Serious immune reaction called 'cytokine release syndrome' (CRS) that may cause fever, low blood pressure, chills, low level of oxygen in the blood, headache, and fast heartbeat		✓	✓
Low levels of a type of white blood cell (neutropenia)		✓	✓
Low number of 'platelets' (cells that help blood to clot, thrombocytopenia)		✓	✓
Problems with the mouth and swallowing, such as change in sense of taste, dry mouth, difficulty swallowing, and sores in the mouth		✓	✓
Infection that may cause fever, chills, shivering, cough, shortness of breath, rapid breathing, and rapid pulse		✓	✓
Skin problems, such as skin rash		✓	✓
COMMON (may affect up to 1 in 10 people)			
Effects on your nervous system. These may be signs of a serious immune reaction called 'immune effector cell associated neurotoxicity syndrome' (ICANS). Some of the symptoms are feeling confused, being less alert or aware, feeling disoriented, feeling sleepy, feeling sleepy with low energy, and slow and difficulty thinking.		✓	✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Talvey will be stored at the healthcare facility by your healthcare professional.

Do not use the medicine after the expiry date which is stated on the carton after "EXP". The expiry date refers to the last day of that month.

If you want more information about Talvey:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website https://www.janssen.com/canada, or by calling 1-800-567-3331.

This leaflet was prepared by Janssen Inc., Toronto, Ontario M3C 1L9.

Last Revised