▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – AMTAGVI® (LIFILEUCEL)

WARNING: TREATMENT-RELATED MORTALITY, PROLONGED SEVERE CYTOPENIA, SEVERE INFECTION, INTERNAL ORGAN HAEMORRHAGE, CARDIOPULMONARY and RENAL IMPAIRMENT

Severe and fatal adverse reactions have occurred in patients treated with the AMTAGVI regimen, including:

- **Prolonged severe cytopenia and severe infections.**
- **Internal organ hemorrhage**
- **Cardiopulmonary impairment**
- **Renal impairment**

AMTAGVI is administered as a one-time treatment in an authorised treatment centre under the supervision of a physician experienced in the use of anti-cancer agents.

1 NAME OF THE MEDICINE

lifileucel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

AMTAGVI lifileucel dispersion for infusion.

Each patient-specific infusion bag of AMTAGVI contains lifileucel at a batch-dependent concentration of TIL. The medicinal product is a cell dispersion for infusion packaged in 1 to 4 intravenous infusion bag(s) containing a total of 1.8 - 100 × 10^9 viable cells suspended in a cryopreservative solution.

Each bag contains approximately 100 mL of dispersion for infusion. AMTAGVI also contains dimethyl sulfoxide (DMSO) and may contain traces of gentamicin and streptomycin (**see section 4.3**).

Excipients with known effect

100 mL of dispersion contain 5,500 mg of DMSO, 280 mg of sodium and 97 mg of potassium.

For the full list of excipients, see **Section 6.1 List of excipients**.

3 PHARMACEUTICAL FORM

A colourless to dark yellow dispersion for infusion.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATION

AMTAGVI is an autologous T cell immunotherapy indicated for the treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

This indication has been approved based on tumour objective response rate (ORR) and duration of response (DOR). A survival benefit has not yet been demonstrated.

4.2 DOSE AND METHOD OF ADMINISTRATION

AMTAGVI must be administered in an authorised treatment centre.

Therapy should be initiated under the direction and supervision of a healthcare professional experienced in the treatment of malignancies and trained for administration and management of patients treated with AMTAGVI. All patients should receive AMTAGVI and IL-2 (aldesleukin) in the authorised treatment centre. Hospitalisation for the lymphodepleting regimen may be based on institutional standards.

Dosage Adults (≥ 18 years)

AMTAGVI is intended for autologous use only.

Treatment consists of a single dose for infusion containing a dispersion of TIL in 1 to 4 patient-specific intravenous infusion bag(s) in individual protective metal cassettes.

Each dose contains 1.8 - 100 × 10^9 viable cells.

Method of administration

AMTAGVI is for intravenous use only.

Pretreatment (lymphodepleting preparative regimen)
Availability of AMTAGVI and interleukin-2 (IL-2, aldesleukin) must be confirmed prior to starting the lymphodepleting regimen. In Australia, it takes approximately 34 days from the time the tumour tissue is received at the manufacturing centre until AMTAGVI is available to be shipped back to the authorised treatment centre, but the time may vary. Administer a lymphodepleting chemotherapy regimen of cyclophosphamide 60 mg/kg intravenously with Mesna (sodium 2-mercaptoethanesulfonate) (per institutional standard or the product information) daily for 2 days followed by fludarabine 25 mg/m^2 intravenously daily for 5 days before infusion of AMTAGVI.

AMTAGVI is recommended to be infused after 24 hours have elapsed, following the last dose of fludarabine, but no later than 4 days. If there is a delay of more than 4 days, the healthcare provider should contact IOVANCE AUSTRALIA PTY LTD.

Premedication
It is recommended that pre-medication with intravenous paracetamol and diphenhydramine or another H1-antihistamine be administered 30 to 60 minutes before the infusion of AMTAGVI to reduce the possibility of an allergic reaction to the infusion **(see section 4.4)**.

Avoid prophylactic use of systemic corticosteroids because their use may interfere with the activity of AMTAGVI (**see section 4.5**).

Precautions to be taken before handling or administering AMTAGVI

AMTAGVI contains human cells. Follow universal and local biosafety guidelines applicable for the handling and disposal of AMTAGVI to avoid potential transmission of infectious diseases.

Preparation prior to administration
Consider total number of AMTAGVI infusion bag(s) when coordinating the timing of AMTAGVI thaw and infusion. Confirm the infusion time in advance and adjust the start time for thawing so that AMTAGVI is available for infusion when the patient is ready. Once 1 bag of AMTAGVI is thawed, the infusion should be started as soon as possible, and each bag must be completed within 3 hours at room/ambient temperature (18 °C to 25 °C). There should not be long delays between the end of infusion of one bag and the start of infusion of a subsequent bag; it is recommended that the duration between infusion bags be within approximately 15 minutes of each other, unless the patient is showing signs of infusion reactions that require additional time for monitoring and management.

- AMTAGVI is for autologous use only. Prior to preparation, match the recipient's identity with the patient identifiers on the cassette label. Do not remove the infusion bag from the cassette if the patient identifiers on the cassette label do not match the intended patient. Contact IOVANCE AUSTRALIA PTY LTD if there are any discrepancies.
- Once patient identification on the cassette is confirmed, remove the infusion bag from the cassette. Check that the patient identifiers on the cassette label match the patient identifiers on the infusion bag label, and match the patient's identity with the patient identifiers on the infusion bag label. Contact IOVANCE AUSTRALIA PTY LTD if there are any discrepancies.
- The number of infusion bag(s) must be checked to ensure correct dose.
- Inspect each bag for any breaks or cracks prior to thawing. Inspect the spike ports for any damage prior to thawing. If a bag is compromised, do not infuse the contents and contact IOVANCE AUSTRALIA PTY LTD.

Thawing
- Thaw and infuse 1 bag at a time. If more than 1 bag has been provided, wait to thaw the next bag until the previous bag has been safely and completely administered.
- Place the infusion bag inside a second sealable bag (preferably sterile) per local guidelines to protect ports from contamination and in case of a leak of the bag.
- Thaw AMTAGVI at approximately 37°C ± 2°C (35-39°C) using either a water bath or a dry thaw method until there are no visible ice or frozen contents in the infusion bag. Total time from start of thawing until completion of thawing should be no more than 10 minutes.
- Immediately remove bag from thawing device; do not store bag at 37 °C. Remove the infusion bag from the sealable plastic bag and wipe dry. Do not wash, spin down, or resuspend AMTAGVI in new media prior to infusion.
- Prior to infusion, inspect the content of the thawed infusion bag. If cell agglomerates are visible, gently mix the content of the bag by inverting the bag prior to infusion and if needed, gently massage the cell agglomerates. Do not shake the bag. Do not infuse the contents of an infusion bag if it is damaged or leaking, or otherwise appears to be compromised

Administration

- AMTAGVI must not be irradiated.
- AMTAGVI is infused immediately after thawing and should be no longer than 30 minutes from time of thaw to infusion.
- Confirm the patient's identity matches with the patient identifiers on the infusion bag.
- A Y-type blood filter with a pore size in the range of 150-260 microns is required. Do NOT use a leukocyte-depleting filter.
- Prime the tubing prior to infusion with sodium chloride 9 mg/mL (0.9 %) solution for infusion.
- Initiate the infusion as soon as possible after thawing and infuse the entire contents of each bag within 3 hours.
- Administer AMTAGVI by gravity at an infusion rate of approximately 1 mL per minute for the initial 5 minutes; thereafter 5 to 10 mL per minute.
- Contents of all bags must be infused to complete a single dose. After the last bag is infused, rinse the tubing with normal saline at the same infusion rate to ensure all product is delivered.

Administration of IL-2 (aldesleukin)

- Beginning 3 to 24 hours after AMTAGVI infusion, administer intravenous IL-2 (aldesleukin) at 600 000 IU/kg every 8 to 12 hours, for up to a maximum of 6 doses to support cell expansion *in vivo*. IL-2 (aldesleukin) should be administered (per institutional standard or the product information) in an authorised treatment centre under the supervision of a physician experienced in the use of anticancer agents
- Patients should remain at the authorised treatment centre until they have completed the IL-2 (aldesleukin) treatment and have recovered from any serious side effects associated with the AMTAGVI treatment regimen.

Monitoring

Prior to and during infusion of AMTAGVI, appropriate emergency medications (e.g., epinephrine and diphenhydramine) should be available at the bedside in case of hypersensitivity reaction, and institutional emergency guidelines should be followed as needed (**see section 4.4**).

Patients must be monitored at the authorised treatment centre following infusion of AMTAGVI and IL-2 (aldesleukin) for signs of potential capillary leak syndrome, neurologic events and other toxicities. Patients may be discharged from the authorised treatment centre once deemed to be recovered from the acute effects of IL-2 (aldesleukin) at the physician's discretion.

Special populations

Elderly (65 years of age or older)

No dose adjustment is required in patients ≥ 65 years of age (**see section 5.1**).

Paediatric population (17 years of age or younger)

The safety and efficacy of AMTAGVI have not been established in paediatric patients. No data are available.

Hepatic and renal impairment

Hepatic and renal impairment studies were not performed; and therefore, no data are available.

The AMTAGVI regimen is not expected to be used in patients with renal or hepatic impairment given the precautions that need to be taken with fludarabine and IL-2 (aldesleukin) for these patient populations.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance(s) or to any of the excipients listed in **section 6.1**.

Contraindications of the lymphodepleting preparative regimen and IL-2 (aldesleukin) must be considered.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Autologous use

AMTAGVI is intended solely for autologous use and must not, under any circumstances, be administered to other patients. AMTAGVI must not be administered if the information on the product labels on the cassette and infusion bags does not match the patient's identity.

Treatment-related mortality

The AMTAGVI regimen (lymphodepletion, AMTAGVI infusion, and IL-2 aldesleukin infusion) is associated with treatment-related mortality. In the clinical trial, the treatment-related mortality rate was 7.5% (N=160), including 2 deaths during the lymphodepleting period, 6 deaths within 30 days, and 4 deaths 38 to 150 days following AMTAGVI infusion. Because clinical trials are conducted under widely varying conditions, treatment-related mortality rates observed in the clinical trials of a drug may not reflect the rates observed in practice.

Cardiac disorder

Severe cardiac disorders, including life-threatening or fatal reactions, have occurred in patients after receiving the AMTAGVI regimen. Serious cardiac disorders included acute myocardial infarction, arrhythmia, and atrial fibrillation. Cardiac arrhythmia resulted in one death among melanoma patients who received the AMTAGVI regimen.

Patients should be monitored for signs and symptoms of cardiac disorder before and after administration of the AMTAGVI regimen. If there is evidence of significant cardiac dysfunction, IL-2 (aldesleukin) should be withheld or discontinued.

Internal Organ Haemorrhage

Patients treated with AMTAGVI may exhibit internal organ haemorrhage. Intra-abdominal and intracranial haemorrhage can be life-threatening and have been associated with at least two deaths in patients who received AMTAGVI. Withhold or discontinue the AMTAGVI regimen if internal organ haemorrhage is indicated, or the patient is deemed ineligible for IL-2 (aldesleukin) infusion. Patients with persistent or repeated thrombocytopenia after receiving AMTAGVI should not use anticoagulants or must be under close monitoring if the patient must take anticoagulants.

Serious infections

Due to the immunosuppressive effects of the lymphodepleting chemotherapy, the AMTAGVI regimen should not be administered to patients with active infections. Severe infections, including life-threatening or fatal infections, have occurred in patients after receiving the AMTAGVI regimen. Patients should be monitored for signs and symptoms of infection before and after the AMTAGVI infusion and treated appropriately. Prophylactic,

pre-emptive, or therapeutic antimicrobials should be administered according to institutional guidelines.

Cytokine release syndrome

Cytokine release syndrome has occurred following administration of the AMTAGVI regimen. In clinical studies, the median time to onset of CRS following AMTAGVI infusion, any grade, was 3 days (range: 1 to 10 days).

Monitoring and management of cytokine release syndrome

Cytokine release syndrome should be identified based on clinical presentation. Patients should be evaluated for other causes of fever, hypoxia, and hypotension, including capillary leak syndrome, sepsis, tumour progression, heart failure, thromboembolism, and allergic reaction.

Patients should be monitored for the first 4 days following the lifileucel infusion at the authorised treatment centre for signs and symptoms of cytokine release syndrome. After the first 4 days following infusion, the patient should be monitored at the physician's discretion.

Mild cytokine release syndrome can often be managed with supportive care, such as fluids and antipyretics. Severe cytokine release syndrome may require aggressive interventions, including corticosteroids and anti-cytokine medications like tocilizumab.

Capillary leak syndrome

Capillary leak syndrome, which was sometimes severe, occurred following treatment with the lifileucel regimen. The median time to onset after administration of lifileucel was 10 days (range: 2 to 20 days) (**see section 4.8**). Capillary leak syndrome can occur secondary to the administration of IL-2 (aldesleukin) as part of the lifileucel regimen, is characterised by hypotension, dyspnoea, oedema, and hypoalbuminemia, and can result in end organ toxicity including cardiac, respiratory, renal, and hepatic toxicity.

IL-2 (aldesleukin) should not be administered to patients with significant cardiac, pulmonary, renal, or hepatic impairment. Use of IL-2 (aldesleukin) should be avoided with other products known to cause hypotension including antihypertensive drugs, those that cause renal toxicity, or hepatotoxicity.

Capillary leak syndrome may begin immediately after IL-2 (aldesleukin) treatment is initiated. Patients should be monitored for signs and symptoms of capillary leak syndrome including assessments of vital signs, weight, fluid intake, albumin levels and urine output.

IL-2 (aldesleukin) should be withheld or discontinued for failure to maintain organ perfusion as demonstrated by altered mental status, reduced urine output, oxygen saturation <90 %, a fall in the systolic blood pressure below 90 mmHg, or onset of cardiac arrhythmias. If capillary leak syndrome is suspected, standard management for capillary leak syndrome should be initiated, which may include intensive care.

Neurological toxicity - including immune effector cell-associated neurotoxicity syndrome (ICANS) and encephalopathy

Neurological toxicities, such as mental status changes, speech difficulties, cortical blindness, limb or gait ataxia, hallucinations, agitation, obtundation, demyelinating polyneuropathy, coma and immune effector cell-associated neurotoxicity syndrome (ICANS), which were sometimes severe, can occur following treatment with the AMTAGVI regimen. The median time to onset of serious neurological adverse reactions following AMTAGVI infusion was 10.5 days (range: 4 to125).

Patients should be monitored for signs and symptoms of neurological toxicity during treatment with the AMTAGVI regimen. Aldesleukin should be discontinued in patients developing moderate to severe lethargy or somnolence, coma or toxic psychosis or for repetitive or difficult to control seizures.

Central nervous system metastases should be evaluated and treated prior to initiation of the AMTAGVI regimen. If possible, concomitant use of the AMTAGVI regimen with other products with a known potential to cause neurotoxicity, or use of the AMTAGVI regimen in patients with seizure disorders or abnormal intracranial imaging should be avoided.

Acute renal failure/Acute kidney injury

Patients treated with the AMTAGVI regimen may develop worsened renal function which has been associated with deaths (**see section 4.8**). Monitor patients with signs and symptoms of acute renal failure before and after infusion of the AMTAGVI regimen. Withhold or discontinue the AMTAGVI regimen if severe acute renal injury is indicated, or the patient is deemed ineligible for IL-2 (aldesleukin) infusion.

Prolonged cytopenias

Patients may exhibit serious or prolonged cytopenia following lymphodepleting chemotherapy and the AMTAGVI infusion (**see section 4.8**). Blood counts should be monitored prior to and after the AMTAGVI infusion. Cytopenias should be managed according to institutional guidelines (i.e., use of filgrastim for neutropenia or transfusion support).

Uveitis

Uveitis, which was sometimes severe, occurred following treatment with the lifileucel regimen. The median time to onset from the start of NMA-LD was 24 days (range: 13 to 127) (**see section 4.8**).

The lifileucel regimen should not be administered to patients with active uveitis. Active uveitis should be ruled out in patients with a history of uveitis prior to administration of the lifileucel regimen. After receiving the lifileucel regimen, patients should be monitored for signs and symptoms of uveitis, which can include blurred vision, eye pain, nyctalopia, photopsia, retinal haemorrhage, or vitreous floaters. Patients presenting with symptoms of uveitis should be evaluated by a trained eye specialist and managed according to current treatment guidelines to prevent any potential severe long-term effects.

Acute respiratory failure

Patients treated with AMTAGVI may develop worsened respiratory function which has been associated with deaths. Monitor patients with signs and symptoms of respiratory failure before and after the AMTAGVI infusion. Withhold or discontinue the AMTAGVI regimen if severe acute respiratory failure is indicated, or the patient is deemed ineligible for IL-2 (aldesleukin) infusion.

Hypersensitivity reactions

Allergic reactions may occur with the infusion of AMTAGVI. Serious hypersensitivity reactions, including anaphylaxis, may be due to DMSO or residual gentamicin and streptomycin in AMTAGVI. Patients not previously exposed to DMSO, gentamicin, or streptomycin should be observed closely. It is recommended that pre-medication with intravenous paracetamol and diphenhydramine or another H1-antihistamine be administered

30 to 60 minutes before the infusion of AMTAGVI to reduce the possibility of an allergic reaction to the infusion.

Acute infusion reactions (defined as occurring within 1 day of infusion) to AMTAGVI may manifest as fever, rigors or chills, tachycardia, rash, hypotension, dyspnoea, cough, chest tightness, or wheezing. These events generally resolve on the same day of infusion. Patients should be monitored during and after the AMTAGVI infusion for signs and symptoms of a severe reaction and treated promptly. If a severe reaction occurs, treatment should be administered per institutional guidelines.

Nonserious allergic reactions may also occur during the administration of the lymphodepleting preparative regimen of cyclophosphamide and fludarabine.

Use in the elderly

Of 156 patients with unresectable or metastatic melanoma who were treated with AMTAGVI in the C-144-01 clinical study, 37 patients (23.5%) were 65 years of age or older. No differences in safety or effectiveness were observed between elderly patients and younger patients.

Paediatric use

The safety and efficacy of AMTAGVI have not been established in paediatric patients. No data are available.

Effects on laboratory tests

See Adverse effects (Undesirable effects) (4.8), Table 1.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed.

Live vaccines

The safety of immunisation with live viral vaccines during or following treatment with AMTAGVI has not been studied. As a precautionary measure, vaccination with live vaccines is not recommended 28 days prior to the start of lymphodepleting chemotherapy, during AMTAGVI treatment, and 3 months following treatment.

Lymphodepleting preparative regimen and IL-2

Interactions with other medicinal products and other forms of interaction of the lymphodepleting preparative regimen and IL-2 (aldesleukin) must be considered.

Corticosteroids

The use of systemic corticosteroids is not recommended starting 21 days prior to starting lymphodepleting chemotherapy, during treatment, and up to 60 days post-AMTAGVI infusion. Prophylactic use of systemic corticosteroids was not allowed under any circumstances. Such medications should only be used to treat immediate life-threatening conditions.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effect of AMTAGVI on fertility.

Use in pregnancy – Pregnancy Category C

There are no available data on lifileucel use in pregnant women and no animal reproductive and developmental toxicity studies have been conducted to assess whether lifileucel can cause fetal harm when administered to a pregnant woman. However, lifileucel is administered with cyclophosphamide, fludarabine, and IL-2 (aldesleukin), which have the potential to cause fetal harm or loss of pregnancy and carry different recommendations regarding pregnancy. Please refer to the respective Product Information documents of other medications in the treatment regimen, if needed. Therefore, the lifileucel regimen is not recommended for women who are pregnant or for women of childbearing potential not using contraception. Women must be advised that they should not become pregnant during the treatment and for a period of 12 months following discontinuation of the therapy.

Use in lactation

There is no information regarding the presence of lifileucel in human milk, the effects on the breastfed infant, and the effects on milk production; however, lifileucel is administered with cyclophosphamide, fludarabine, and IL-2 (aldesleukin), which have the potential to cause serious adverse reactions in breastfed infants. Therefore, breastfeeding should be discontinued during treatment with the lifileucel regimen. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from AMTAGVI therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The AMTAGVI treatment regimen has a major influence on the ability to drive and use machines. Dizziness (common), tiredness (very common), or weakness (very common) are possible side effects (**see section 4.8**). Additionally, neurological toxicities have been observed with the administration of IL-2 (aldesleukin), including delirium (common), encephalopathy (common), and depressed level of consciousness (uncommon).

Due to the potential for events that may impact the patient's ability to drive and use machines, patients should refrain from driving or operating heavy or potentially dangerous machines for at least 3 weeks after infusion.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety data described in this section reflect exposure to AMTAGVI within a regimen that included cyclophosphamide, fludarabine, and IL-2 (aldesleukin) in Cohorts 2 and 4 of study C-144-01, an open-label, multicenter, multicohort, single-arm study in which 156 adult patients with unresectable or metastatic melanoma received a single infusion of autologous TIL.

The most common adverse events (≥ 20 %) included thrombocytopenia (87.8 %), leukopenia (84.6 %), anaemia (82.7 %), chills (76.9 %), nausea (74.4 %), electrolyte imbalance (71.2 %), pyrexia (69.2 %), fatigue (62.2 %), arrythmia (58.3 %), oedema (57.7 %), diarrhoea (53.8 %), rash (50.6 %), febrile neutropenia (47.4 %), vomiting (46.8 %), dyspnoea (43.6 %), hypotension (42.3 %), musculoskeletal pain (39.7 %), appetite disorder (37.8 %), headache (37.2 %), infections – pathogen unspecified (35.9 %), hepatic enzyme abnormal (35.3 %), changes in weight (34.6 %), haemorrhage (32.7 %), alopecia (31.4 %), cough (26.9 %), hypoproteinaemia (26.9 %), hypoxia (26.3 %), acute kidney injury (24.4 %), insomnia (24.4 %), encephalopathy (23.1 %), hypertension (22.4 %), infections – bacterial (21.2 %), pruritus (20.5 %) Other common adverse events reported at a lower frequency and considered clinically important included delirium (15.4 %), capillary leak syndrome (13.5 %), sepsis

(7.1 %), infusion related reaction (6.4 %), uveitis (5.1 %), and cytokine release syndrome (3.2 %).

The most common serious adverse events (≥ 2 %) included infections – pathogen unspecified (8.3 %), dyspnoea (7.1 %), febrile neutropenia (6.4 %), thrombocytopenia (5.8 %), haemorrhage (5.1%), sepsis (5.1 %), acute kidney injury (3.8 %), pyrexia (3.8 %), anaemia (3.2 %), encephalopathy (3.2 %), oedema (3.2 %), hypotension (2.6 %), infections – viral (2.6 %), leukopenia (2.6 %), and pleural effusion (2.6 %). Other common serious adverse events reported at a lower frequency and considered clinically important include hypoxia (1.9 %), anaphylactic reaction (1.3 %), arrhythmia (1.3 %), capillary leak syndrome (1.3 %), delirium (1.3 %), pancytopenia (1.3 %), cytokine release syndrome (0.6 %), infusion related reaction (0.6 %), and uveitis (0.6 %).

The most common (≥ 5 %) severe adverse events (NCI CTCAE Grade ≥ 3) included leukopenia (82.1 %), thrombocytopenia (80.8 %), anaemia (67.9 %), febrile neutropenia (47.4 %), electrolyte imbalance (37.8 %), infections – pathogen unspecified (16.7 %), hypotension (13.5 %), hypoxia (12.8 %), hypertension (12.2 %), rash (12.2 %), dyspnoea (11.5 %), pyrexia (11.5 %), hepatic enzyme abnormal (9.6 %), acute kidney injury (8.3 %), infections – bacterial (8.3 %), fatigue (7.7 %), encephalopathy (7.1 %), haemorrhage (7.1 %), oedema (7.1 %), sepsis (7.1 %), arrhythmia (6.4 %), musculoskeletal pain (6.4 %), capillary leak syndrome (5.1 %), chills (5.1 %), and pancytopenia (5.1 %).

Tabulated list of adverse reactions

Table 1 summarises the adverse reactions that were reported in patients treated with the AMTAGVI regimen for the duration of the study. The adverse reaction profile was consistent with adverse reactions expected in patients treated with cyclophosphamide, fludarabine, and IL-2 (aldesleukin). When assessing the safety of the AMTAGVI regimen, the safety profile and product information of these medicinal products should also be considered.

Adverse reactions are listed by MedDRA body system organ class and by frequency. Frequencies are defined as: very common (≥ 1 / 10); common (≥ 1 / 100 to <1 / 10); uncommon (≥ 1 / 1 000 to <1 / 100); rare (≥ 1 / 10 000 to <1 / 1 000); very rare (<1 / 10 000); not known (cannot be estimated from the available data).

Table 1 Summary of adverse events observed in patients treated with AMTAGVI (N=156)

System Organ Class	Frequency	Adverse Event	Incidence (%)	
			All grades	Grade ≥ 3
Infections and infestations	Very common	Infections – pathogen unspecified	35.9	16.7
		Infections – bacterial	21.2	8.3
	Common	Infections – viral	9.0	3.8
		Sepsis	7.1	7.1
Blood and lymphatic system disorders	Very common	Thrombocytopenia	87.8	80.8
		Leukopenia	84.6	82.1
		Anaemia	82.7	67.9
		Febrile neutropenia	47.4	47.4

System Organ Class	Frequency	Adverse Event	Incidence (%)	
			All grades	Grade ≥ 3
		Pancytopenia	10.3	5.1
	Uncommon	Bone marrow failure	0.6	0.6
Immune system disorders	Common	Cytokine release syndrome	3.2	1.3
		Anaphylactic reaction	1.3	1.3
	Uncommon	Hypersensitivity	0.6	0.6
Metabolism and nutrition disorders	Very common	Electrolyte imbalance[1]	71.2	37.8
		Appetite disorder	37.8	1.9
		Changes in weight	34.6	1.9
		Hypoproteinaemia[2]	26.9	4.5
	Common	Fluid overload	7.1	0
		Hyperglycaemia	7.1	2.6
		Dehydration	5.1	0.6
		Hypoglycaemia	4.5	0.6
		Acidosis	3.8	0.6
Psychiatric disorders	Very common	Insomnia	24.4	0
		Anxiety	18.6	1.3
		Delirium[3]	15.4	3.8
	Common	Depression	5.8	0.6
Nervous system disorders	Very common	Headache	37.2	1.3
		Encephalopathy[4]	23.1	7.1
		Dizziness	14.7	1.9
		Neuropathy peripheral[5]	12.8	1.9
	Common	Dysgeusia	8.3	0
		Aphasia[6]	3.8	0.6
Eye disorder	Common	Visual impairment	9.0	0
		Uveitis	5.1	1.9
		Diplopia	2.6	0.6
		Vitreous floaters	1.9	0
Ear and labyrinth disorders	Common	Hypoacusis	1.9	0
		Tinnitus	1.9	0
		Deafness	1.3	0
Cardiac disorders	Very common	Arrhythmia[7]	58.3	6.4

System Organ Class	Frequency	Adverse Event	Incidence (%)	
			All grades	Grade ≥ 3
	Common	Bradycardia	3.8	0
	Uncommon	Cardiomyopathy	0.6	0.6
Vascular disorders	Very common	Hypotension	42.3	13.5
		Haemorrhage	32.7	7.1
		Hypertension	22.4	12.2
		Capillary leak syndrome	13.5	5.1
	Common	Flushing	9.0	0
		Thrombosis	8.3	1.3
		Embolism	1.9	0
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea[8]	43.6	11.5
		Cough	26.9	0.6
		Hypoxia	26.3	12.8
		Pleural effusion	12.8	2.6
	Common	Oropharyngeal pain	7.1	0
		Nasal congestion	5.8	0
		Rales	3.2	0
		Pulmonary embolism	2.6	2.6
	Uncommon	Pulmonary fibrosis	0.6	0
Gastrointestinal disorders	Very common	Nausea	74.4	3.2
		Diarrhoea	53.8	2.6
		Vomiting	46.8	1.3
		Abdominal pain	19.9	1.3
		Dry mouth	10.9	0
	Common	Oral disorder[9]	8.3	0
		Abdominal distension	4.5	0.6
		Colitis	3.8	1.3
		Ascites	3.2	0.6
		Gastritis	2.6	0
Hepatobiliary disorders	Very common	Hepatic enzyme abnormal[10]	35.3	9.6
		Hyperbilirubinaemia	12.8	2.6
	Uncommon	Drug-induced liver injury	0.6	0.6
Skin and subcutaneous tissue disorders	Very common	Rash	50.6	12.2
		Alopecia	31.4	0

System Organ Class	Frequency	Adverse Event	Incidence (%)	
			All grades	Grade ≥ 3
		Pruritus	20.5	0
		Vitiligo	10.3	0
	Common	Erythema	7.7	0.6
		Dry skin	6.4	0
		Hyperhidrosis	6.4	0.6
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain[11]	39.7	6.4
	Common	Muscular weakness	9.6	1.3
		Muscle spasms	9.0	0
Renal and urinary disorders	Very common	Acute kidney injury[12]	24.4	8.3
		Frequent urination[13]	11.5	0
	Common	Dysuria	7.1	0
		Proteinuria	5.8	0
		Urinary incontinence	5.8	0
		Urinary retention	3.2	0.6
		Bladder spasms	1.9	0.6
General disorders and administration site conditions	Very common	Chills	76.9	5.1
		Pyrexia	69.2	11.5
		Fatigue	62.2	7.7
		Oedema	57.7	7.1
	Common	Mucosal inflammation	7.1	0.6
Investigations	Common	Blood creatine phosphokinase increased	7.7	2.6
		Urine output decreased	4.5	3.8
		Electrocardiogram QT prolonged	3.8	1.9
		C-reactive protein increased	3.2	0
Injury, poisoning and procedural complications	Common	Infusion related reaction	6.4	1.9

[1] Electrolyte imbalance includes electrolyte imbalance, blood calcium decreased, hypocalcaemia, blood potassium decreased, hypokalaemia, blood magnesium decreased, hypomagnesaemia, blood sodium decreased, hyponatraemia, blood phosphorus decreased, hypophosphataemia, hypercalcaemia, hyperkalaemia, hypermagnesaemia, hypernatraemia.

[2] Hypoproteinaemia includes hypoproteinaemia, protein total decreased, blood albumin decreased, hypoalbuminaemia.

[3] Delirium includes hallucination, hallucination, visual, delirium, delusion, disorientation, agitation, restlessness.

[4] Encephalopathy includes depressed level of consciousness, disturbance in attention, encephalopathy, hypoxic-ischaemic encephalopathy, lethargy, memory impairment, somnolence, toxic encephalopathy, mental impairment, confusional state, mental status changes, bradyphrenia.
[5] Neuropathy peripheral includes neuropathy peripheral, hypoaesthesia, paraesthesia, autonomic neuropathy, peripheral motor neuropathy, peripheral sensory neuropathy.
[6] Aphasia includes aphasia, dysarthria.
[7] Arrhythmia includes atrial fibrillation, sinus tachycardia, supraventricular tachycardia, tachycardia, arrhythmia, atrioventricular block second degree, ventricular tachycardia, atrial flutter, extrasystoles, ventricular extrasystoles
[8] Dyspnoea includes acute respiratory failure, dyspnoea, dyspnoea exertional, orthopnoea, respiratory distress, respiratory failure, wheezing, tachypnoea.
[9] Oral disorder includes oral disorder, stomatitis, oral pain, glossitis, mouth ulceration, swollen tongue.
[10] Hepatic enzyme abnormal includes alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, hypertransaminasaemia, gamma-glutamyltransferase increased, hepatic enzyme increased, liver function test increased, transaminases increased.
[11] Musculoskeletal pain includes back pain, myalgia, neck pain, pain in extremity, pain in jaw, non-cardiac chest pain, pain, arthralgia, arthritis, bone pain, flank pain, musculoskeletal chest pain, musculoskeletal discomfort.
[12] Acute kidney injury includes blood creatinine increased, acute kidney injury, oliguria, renal failure, renal tubular necrosis.
[13] Frequent urination includes nocturia, pollakiuria, polyuria.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There are no data regarding overdose with AMTAGVI.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Tumour infiltrating lymphocytes (TIL) are cytotoxic and helper T cells that infiltrate tumours as a component of the immunological response to a patient's cancer. Following manufacturing and infusion billions of polyclonal, patient specific TIL migrate to tumour sites, in which they recognise and target a multitude of individualised, tumour specific neoantigens. Tumour neoantigens are mutated antigens, presented by human leukocyte antigen (HLA) on the surface of the tumour. TIL recognise the tumour-specific neoantigens via T-cell receptor (TCR)-peptide human leukocyte antigen (pHLA) engagement. The TCR-pHLA interaction induces T cell activation and T cell-mediated tumour killing via secretion of cytokines and cytolytic enzymes and cell-mediated killing.

The specific mechanism of action of AMTAGVI (lifileucel) is unknown.

Pharmacodynamic effects

The pharmacodynamic activity of lifileucel was explored by measuring longitudinal changes of cytokines and chemokines in the peripheral blood at baseline (prior to lymphodepletion)

and up to 84 days following the lifileucel infusion. Cytokines and chemokines measured included IL-15, IL-6, IL-7, IL-9, IL-10, IL-12 (p40), C-C motif chemokine ligand 2 (CCL2), C-X-C motif chemokine ligand 10 (CXCL10), interferon gamma (IFN-γ), and tumour necrosis factor alpha (TNF-α).

Both IL-15 and CXCL10 levels peaked around Day 1 to Day 4 following the lifileucel infusion, decreased over time, and returned to baseline levels within 1 to 3 months. This was consistent with the proposed mechanism of lymphodepletion for IL-15 and suggested that CXCL10, which has a role in the recruitment of immune cells to site of inflammation and tumours, may have the potential to serve as a PD marker for TIL activity. At Day -7, prior to lymphodepletion, serum IFN-γ levels were low to negligible, increasing at Day 1, peaking at Day 4, before returning to baseline levels (Day -7), at Day 14. The increase in circulating IFN-γ, is indicative of T-cell activation of the infused cells. Other cytokines and chemokines listed above did not show any noticeable changes.

Clinical trials

The efficacy of a single treatment with AMTAGVI was evaluated in Study C-144-01, a global, multicentre, multicohort, open-label, single-arm clinical trial (NCT02360579).

The study enrolled patients with unresectable or metastatic melanoma (Stage IIIc or Stage IV per the American Joint Committee on Cancer staging manual, 7th edition) who have progressed following at least 1 systemic therapy, including a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor or BRAF inhibitor with MEK inhibitor. Other enrolment criteria included Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, adequate function of organs, including bone marrow, kidneys and liver. The study excluded patients with melanoma of uveal or ocular origin, symptomatic and/or untreated brain metastases, organ allograft or prior cell transfer, chronic systemic steroid therapy, active systemic infections, any form of primary or acquired immunodeficiency, coagulation disorders, Grade 2 or higher haemorrhage within 14 days prior to enrollment (tumour resection), left ventricular ejection fraction less than 45% or New York Heart Association functional classification greater than Class 1, and forced expiratory volume in one second of less than or equal to 60%.

Of the 111 patients in the primary efficacy cohort who underwent tumour resection, 22 patients (19.8%) who underwent tumour harvest did not receive lifileucel. The reasons for not receiving lifileucel included: inability to manufacture AMTAGVI (n=6), disease progression (n=5), death due to disease progression (n=3), start of a new anticancer therapy (n=2), fatal adverse event (AE) related to the lymphodepleting regimen (n=1), AE (n=1), withdrawal of consent and physician's decision (n=2), and meeting the exclusion criteria (n=2).

Among the 89 patients who received AMTAGVI, 2 patients received AMTAGVI that did not meet the protocol pre-specified product specification. There were 87 patients in the efficacy analysis population. The median (min, max) time between tumour harvest and AMTAGVI infusion was 34 days (26, 99). The median (min, max) duration of the manufacturing process was 23 days (23, 43). Lesion origin of AMTAGVI products included skin, lymph nodes, liver, lung, peritoneal, musculo skeletal, breast, and others.

Of the 87 patients, 87 (100%) received prior anti-PD-(L)1 therapy, 86 (98.9%) had progressive disease for at least a prior anti-PD-(L)1 therapy, 72 (82.8%) received prior anti-CTLA-4 therapy, 68 (78.2%) had progressive disease for at least a prior anti-CTLA-4 therapy, 48 (55.2%) received anti-PD-1/anti-CTLA-4 combination therapy and 24 (27.6%) received a BRAF inhibitor or combination therapy with BRAF and MEK inhibitors. Patients

received a median of 3 prior lines of therapy (min, max: 1, 8). The median age was 58 years (min, max: 25, 74 years), with 25.3% age 65 or older, 50.6% were male, 95.4% were white, 2.3% were black, and 1.1% were Asian. Disease characteristics were: Stage IV: 98.9%, BRAF V600 mutation-positive: 27.6%; PD-L1 TPS ≥5%: 23.0%; elevated LDH: 64.4%; brain and/or liver metastases: 50.6%. The median target lesion sum of diameters was 99.5 mm (min, max: 15.7, 552.9). The median number of target and non-target lesions as defined by RECIST 1.1 was 6 (min, max: 1, 16). The performance status prior to tumour procurement was ECOG 0 (71.3%) and ECOG 1 (28.7%).

AMTAGVI was administered following a lymphodepleting regimen consisting of cyclophosphamide 60 mg/kg daily with mesna for 2 days followed by fludarabine 25 mg/m^2 daily for 5 days. Three (3) to 24 hours after AMTAGVI infusion, IL-2 (aldesleukin) was administered at 600,000 IU/kg every 8 to 12 hours for up to 6 doses to support cell expansion in vivo. The median AMTAGVI administered dose was 20.5 × 10^9 viable cells (min, max: 1.3 x 10^9, 72.0 x 10^9). The median number of administered IL-2 (aldesleukin) doses was 6, with 36.8% receiving between 1 and 5 doses of IL-2.

The primary endpoint was objective response rate (ORR) by the Independent Review Committee (IRC) per RECIST v1.1. Secondary endpoints included duration of response (DoR). Efficacy results are summarised in Table 2.

Table 2 Efficacy Results in Study C-144-01 primary efficacy cohort

Endpoint[a]	**Efficacy Set (N=87)**
Objective Response Rate	
ORR, % (95% CI)[b]	28.7 (19.5, 39.4)
Complete response, n (%)	4 (4.6)
Partial response, n (%)	21 (24.1)

CI, confidence interval; ORR, objective response rate.
[a] Per RECIST v1.1 assessed by Independent Review Committee (IRC).
[b] Number of responders was N=25.

The median time to first response to AMTAGVI was 1.5 months (min, max: 1.3, 4.2). With a median follow-up of 44.0 months, the median DoR was 10.4 months (95% CI: 4.1, 26.2; min, max: 1.4+, 45.8+).

Supporting pooled efficacy analysis included 189 patients who underwent tumour resection of whom 33 (17.5%) did not receive lifileucel. The reasons for not receiving lifileucel included: inability to manufacture AMTAGVI (n=8), disease progression (n=9), death due to disease progression (n=4), start of a new anticancer therapy (n=2), fatal AE related to the lymphodepleting regimen (n=2), AE (n=2), withdrawal of consent and physician's decision (n=3), and meeting the exclusion criteria (n=3).

Among the 156 patients who received AMTAGVI, 2 patients who received AMTAGVI that did not meet the protocol pre-specified product specification and 1 patient who received AMTAGVI below the protocol pre-specified dosing range due to anaphylactic reaction were excluded.

The supporting pooled efficacy set included 153 patients. The median administered AMTAGVI dose was 21.1× 10^9 viable cells (min, max: 1.2 x 10^9, 99.5 x 10^9) and the median number of administered IL-2 (aldesleukin) doses was 6 with 43.1% receiving between 1 and 5 doses of IL-2. The ORR was 31.4% (95% CI: 24.1%, 39.4%) with a CR of 5.9% (n=9) and

PR of 25.5% (n=39). The median time to initial response to AMTAGVI was 1.4 months (min, max: 1.3, 4.2). With a median follow-up of 57.9 months at the completion of the study, the median DOR as assessed by the IRC per RECIST v1.1 was 36.5 months (min, max: 1.4+, 58.7+). Fifteen responders (31.3%) completed the 5-year assessment with an ongoing response.

5.2 PHARMACOKINETIC PROPERTIES

The cellular nature of AMTAGVI prevents conduction of conventional pharmacokinetic (PK) studies of absorption, distribution, metabolism, and excretion. Persistence of unique T-cell receptor (TCR) clonotypes from AMTAGVI lots in the peripheral blood were tracked for pharmacokinetic activity.

The proportion of unique TCR clonotypes from the AMTAGVI lots contributing to the peripheral blood TCR repertoire among infused patients was analysed using a semi-quantitative polymerase chain reaction followed by next generation sequencing. The proportion of TCR clones that are composed of clonotypes identified in the product increases from a mean of 14% (n=95) at Enrollment to 83% at Day 4 after AMTAGVI infusion. The TCR clones declined to 51% at Day 14 (n=96) and remained between 37% and 41% from Day 42 (n=120) to Month 12 (n=22) post-infusion of AMTAGVI. No significant correlation was found between AMTAGVI persistence and efficacy.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

CryoStor CS10 (contains dimethyl sulfoxide (DMSO))

Multiple Electrolytes Injection, Type 1, USP (Plasma-Lyte A)

Human serum albumin (HSA)

Interleukin-2

Water for injections

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

1 year at ≤ −150 °C.

After thawing, 3 hours at room temperature (18 °C to 25 °C).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

AMTAGVI must be stored and transported in the vapour phase of liquid nitrogen (≤ −150 °C).

AMTAGVI must remain in the original protective packaging including the cassette and remain frozen until patient is ready for treatment to ensure viable cells are available for administration. Thawed medicinal product should not be refrozen.

For storage conditions after thawing of the medicinal product, see **section 6.3**.

6.5 NATURE AND CONTENTS OF CONTAINER

One individual dose comprises 1 to 4 infusion bags with approximately 100 mL of cell dispersion per bag.

Each ethylene vinyl acetate (EVA) infusion bag is stored and shipped within one protective aluminium cassette and stored in the vapor phase of liquid nitrogen.

One cryoshipper may contain multiple metal cassettes intended for a single patient.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

AMTAGVI (lifileucel) is an autologous cell-based product produced from patient tumour tissue containing viable T cells that are amplified and reinvigorated *ex vivo*. Consequently, a defined structure is not available for lifileucel.

CAS number

No data available.

7 MEDICINE SCHEDULE (POISONS STANDARD)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

04 June 2026 (ARTG 527457)

10 DATE OF REVISION

Not applicable