09-J4000-81

Original Effective Date: 04/01/24

Reviewed: 03/11/26

Revised: 04/15/26

Subject: Lifileucel (Amtagvi) suspension for IV infusion

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration | Position Statement | Billing/Coding | Reimbursement | Program Exceptions | Definitions

Related Guidelines | Other | References | Updates

DESCRIPTION:

Melanoma accounts for less than 2% of all skin cancers as well as all cancer deaths in the United States. However, melanoma may spread quickly; therefore, early diagnosis and treatment are important for improved cure rates. The 5-year survival rates are 99.6% for localized melanomas, 73.9% with regional spread, and 35.1% with distant metastases. Advanced melanoma, also known as unresectable or metastatic disease, are typically treated with immunotherapy with immune checkpoint inhibitors (e.g., ipilimumab, cemiplimab, nivolumab, pembrolizumab) and, if BRAF V600 mutation positive, a BRAF inhibitor (e.g., encorafenib, vemurafenib, dabrafenib) with or without a MEK inhibitor (e.g., trametinib, cobimetinib, binimetinib). Immunotherapies have an initial response rate of about 45% with a relapse rate of 10%, and BRAF/MEK inhibitors effectively shrinking tumors but are associated with higher relapse rates due to resistance. For continued progressive disease, chemotherapy is an option but it demonstrates a limited response rates of 4% to 10% and a median overall survival rate of approximately 7 months.

On February 16, 2024, the FDA approved lifileucel (Amtagvi), which is the first tumor-derived 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 is approved under accelerated approval based on objective response rate (ORR) with continued approval contingent upon verification and description of clinical benefit in a confirmatory trial.

The efficacy and safety of lifileucel (Amtagvi) was evaluated in a multi-center, open-label, single-arm clinical study. Enrolled patients had unresectable or metastatic melanoma previously treated with at least one systemic immunotherapy (i.e., immune checkpoint inhibitors), and if BRAF V600 mutation-positive, a BRAF inhibitor with or without a MEK inhibitor. Excluded patients included those with uncontrolled brain metastases, organ allograft or prior cell transfer, melanoma of uveal or ocular origin, systemic steroid therapy for any reason, Grade 2 or higher hemorrhage within 14 days prior to study enrollment (tumor resection), LVEF less than 45% or NYHA functional classification greater than Class 1, and patients with FEV1 of less than or equal to 60%. There were 111 patients who underwent tumor resection with 22 patients not receiving therapy with lifileucel and 89 patients receiving lifileucel therapy. Of the 89 patients receiving lifileucel therapy, seven were excluded due to product specification/comparability, leaving 82

patients for efficacy evaluation. Among these, 73 patients received the full recommended dosing range of 7.5 x 10^9 to 72 x 10^9 viable cells. The median age was 58 years (range: 25-74 years), and 52.1% were male. As for race, 94.5% were white, 2.7% were black, and 1.4% were Asian. The median target lesion sum of diameters was 108.7 mm (range: 15.7-552.9 mm), and the performance status prior to tumor procurement was ECOG 0 (71.2%) and ECOG 1 (28.8%). Lifileucel 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 to 24 hours after the lifileucel infusion, patients received IL-2 (aldesleukin) at 600,000 IU/kg every 8 to 12 hours for up to 6 doses in order to support cell expansion. The median time to initial response with lifileucel was 1.5 months (range: 1.3- 4.2 months). The objective response rate (ORR) and duration of response (DoR) are provided in Table 1.

Table 1: Objective Response Rate and Duration of Response with Lifileucel Therapy (n=73)

Endpoint[a]	**Data**
Objective Response Rate	
ORR, % (95% CI)	31.5 (21.1, 43.4)
Complete response rate, n (%)	3 (4.1)
Partial response rate, n (%)	20 (27.4)
Duration of Response[b,c]	
Median DoR in months (95% CI)[d]	NR (4.1, NR)
Range[e]	(1.4+, 26.3+)
Patients with DoR ≥ 6 months[f], n (%)	13 (56.5)
Patients with DoR ≥ 9 months[f], n (%)	11 (47.8)
Patients with DoR ≥ 12 months[f], n (%)	10 (43.5)

CI, confidence interval; DoR, duration of response; NR, not reached; ORR, objective response rate.

[a] Per RECIST v1.1 assessed by Independent Review Committee (IRC).

[b] Number of responders was N=23.

[c] Kaplan-Meier estimate of median potential follow-up for DoR was 18.6 months.

[d] Kaplan-Meier estimate in months among all responders. DoR measured from the date of confirmed initial objective response to the date of progression or death from any cause.

[e] + sign indicates a censored value

[f] Observed proportion of patients with duration of response beyond landmark time

A pooled efficacy analysis was also performed and included 189 patients who underwent tumor resection. Among these patients, 156 patients received lifileucel (Amtagvi) therapy. Two patients were excluded (one because of product specification and one below the dosing range due to an anaphylactic reaction). Therefore, the pooled efficacy set included 153 patients. The median administered lifileucel dose was 21.1× 10^9 viable cells and the median number of administered IL-2 (aldesleukin) doses was 6. The ORR was 31.4% (95% CI: 24.1%, 39.4%) with a CR of 5.2% (n=8) and PR of 26.1% (n=40). The median time to initial response was 1.5 months (range: 1.3 - 4.2 months). The median DoR was not reached (range: 1.4+, 45.0+). Among responders, 62.5%, 56.3% and 54.2% maintained durable responses at 6, 9 and 12 months, respectively, following the initial response.

As outline in the lifileucel (Amtagvi) prescribing information, the most common (incidence of greater than or equal to 20%) adverse reactions in order of decreasing frequency were chills, pyrexia, fatigue, tachycardia, diarrhea, febrile neutropenia, edema, rash, hypotension, alopecia, infection, hypoxia, and dyspnea.

POSITION STATEMENT:

The administration of lifileucel (Amtagvi) **meets the definition of medical necessity** when **ALL** of the following are met:

1. Unresectable or metastatic melanoma but not of uveal or ocular origin - medical record documentation supporting the diagnosis must be submitted
2. Member will be 18 years of age or older at the time of the treatment infusion
3. Member has been previously treated with the following ("a" and "b"): - medical record documentation of the member's prior melanoma treatment history must be submitted
    a. Immune checkpoint inhibitor (e.g., ipilimumab, cemiplimab, nivolumab, pembrolizumab)
    b. If BRAF V600 mutation positive, a BRAF inhibitor (e.g., encorafenib, vemurafenib, dabrafenib) with or without a MEK inhibitor (e.g., trametinib, cobimetinib, binimetinib)
4. Following the completion of lymphodepleting chemotherapy, the lifileucel (Amtagvi) infusion will be followed by IL-2 (aldesleukin) therapy at a maximum of 600,000 IU/kg per dose IV for 6 total doses administered within 4 days after the lifileucel (Amtagvi) infusion to support cell expansion
5. Member has met **ALL** the following: - medical record documentation must be submitted
    a. Absolute neutrophil count (ANC) greater than or equal to 1,000 cells/mm^3
    b. Hemoglobin (Hb) greater than or equal to 9.0 g/dL
    c. Platelet count greater than or equal to 100,000 cells/mm^3
6. Member has **NONE** of the following: - medical record documentation must be submitted
    a. Uncontrolled brain metastases
    b. Concomitant systemic steroid therapy for any reason, except for replacement therapy (e.g., prednisone equal to or less than 10 mg/day or equivalent dose) to treat life-threatening conditions (e.g., adrenal insufficiency)
    c. Signs and symptoms of acute renal failure prior to treatment
    d. Hemorrhage (grade 2 or higher) within 14 days prior to treatment
    e. Left ventricular ejection fraction (LVEF) less than 45% or NYHA functional classification greater than Class 1
    f. Forced expiratory volume in one second (FEV1) of less than or equal to 60%
    g. Uncontrolled systemic infection at the time of planned treatment initiation
    h. Previously received tumor-derived autologous T cell immunotherapy (including lifileucel) in their lifetime
7. The healthcare facility where lifileucel will be administered is an Amtagvi Authorized Treatment Center
8. The administration of lifileucel (Amtagvi) will not exceed one single dose as provided by the manufacturer

Approval duration: 3 months to allow for a one-time infusion of therapy

Lifileucel (Amtagvi) is considered **experimental or investigational** for any other indications due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcome.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Lifileucel (Amtagvi) is a tumor-derived 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.
- The lifileucel (Amtagvi) dose is between 7.5×10^9 and 72×10^9 viable cells administered via intravenous infusion. Administration of lifileucel (Amtagvi) should occur in an inpatient hospital setting under the supervision of a physician experienced in the use of anticancer agents. An intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine must be available.
- It is important to confirm the availability of the patient-specific lifileucel (Amtagvi) cassette(s) and infusion bag(s) as well as IL-2 (aldesleukin) prior to starting the lymphodepleting regimen.
- The lymphodepleting chemotherapy regimen is administered prior to lifileucel (Amtagvi) therapy and includes cyclophosphamide 60 mg/kg intravenously with mesna daily for 2 days followed by fludarabine 25 mg/m^2 intravenously daily for 5 days.
- Patients should receive premedication with acetaminophen and diphenhydramine or another H1-antihistamine, approximately 30 to 60 minutes prior to lifileucel (Amtagvi); however, avoid prophylactic use of systemic corticosteroids which may interfere with the activity of lifileucel (Amtagvi).
- Lifileucel (Amtagvi) should be infused as soon as possible after 24 hours have elapsed following the last dose of fludarabine, but no later than 4 days. Prior to the lifileucel (Amtagvi) infusion, prime the tubing with normal saline. Administer lifileucel (Amtagvi) at an infusion rate of approximately 1 mL per minute for the initial 5 minutes; thereafter 5 mL to 10 mL per minute. The 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. Do not use a leukocyte depleting filter while infusing lifileucel (Amtagvi).
- IL-2 (aldesleukin) is administered 3 to 24 hours after the lifileucel (Amtagvi) infusion at 600,000 IU/kg intravenously every 8 to 12 hours for up to a maximum of 6 doses to support cell expansion in vivo. IL-2 (aldesleukin) should also be administered in an inpatient setting under the supervision of a physician experienced in the use of anticancer agents.
- Lifileucel (Amtagvi) is shipped directly to the treatment center in the vapor phase of a liquid nitrogen cryoshipper. All treatment centers should have onsite storage in vapor phase of liquid nitrogen. Product and patient-specific labels are located on both the product infusion bag(s) and protective metal cassette(s), which are inside the liquid nitrogen cryoshipper. Lifileucel (Amtagvi) must be stored frozen in the vapor phase of liquid nitrogen (less than or equal to minus 150°C).
- 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. Once 1 bag of lifileucel (Amtagvi) is thawed, the infusion should be started as soon as possible and must be completed within 3 hours at room or ambient temperature (18°C to 25°C).
- Prior to infusion, inspect the contents of the thawed infusion bag. If cell clumps are visible, gently mix the contents of the bag by inverting the bag prior to infusion. If needed, gently massage the bag to disperse cell clumps. Do not infuse the contents of an infusion bag if it is damaged or leaking, or otherwise appears to be compromised.

Dose Adjustments

- None

Drug Availability

- Lifileucel (Amtagvi) is provided as a single dose for intravenous infusion containing a suspension of tumor-derived T cells. Each dose contains 7.5 x 10^9 to 72 x 10^9 viable cells suspended in a cryopreservation medium.
- The dose is supplied in 1 to 4 infusion bag(s) (NDC 73776-001-11), with each bag containing approximately 100 mL to 125 mL of frozen suspension in 5% DMSO, 0.5% albumin (human), and 300 IU/mL IL-2 (aldesleukin). Each bag is contained within a protective metal cassette (NDC 73776-001-12).

PRECAUTIONS:

Boxed Warning

- **Treatment-related mortality:** Lifileucel (Amtagvi) 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 lifileucel (Amtagvi) administration. Adverse reactions associated with these deaths included severe infections (sepsis, pneumonia and encephalitis), internal organ hemorrhage (abdominal hemorrhage and intracranial hemorrhage), acute renal failure, acute respiratory failure, cardiac arrythmia, extensive ascites, liver injury, and bone marrow failure. 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.
- **Prolonged severe cytopenia:** Patients treated with lifileucel (Amtagvi) may exhibit Grade 3 or higher cytopenia for weeks or longer. Based on adverse event reporting, Grade 3 or higher cytopenia or pancytopenia, which did not resolve to less than or equal to Grade 2 or lasted beyond 30 days post infusion, occurred in 45.5% of melanoma patients who received lifileucel. Prolonged cytopenia included thrombocytopenia (30.1%), lymphopenia (19.9%), neutropenia (17.3%), leukopenia (14.7%), and pancytopenia (1.3%). Monitor blood counts after lifileucel infusion.
- **Severe infection:** Severe, life-threatening, or fatal infections occurred in patients after lifileucel (Amtagvi) infusion. Treatment-related infections (any severity) occurred in 26.9% of patients with melanoma. Grade 3 or higher infections occurred in 13.5% of patients, including 10.9% of patients with infections of an unspecified pathogen and 3.8% of patients with infections of a specified pathogen. Do not administer lifileucel (Amtagvi) to patients with clinically significant systemic infections. Monitor patients for signs and symptoms of infection before and after lifileucel (Amtagvi) infusion and treat appropriately. Administer prophylactic antimicrobials according to institutional guidelines. Febrile neutropenia was observed in 46.8% of patients with melanoma after lifileucel (Amtagvi). In the event of febrile neutropenia, evaluate for infection and manage with broad-spectrum antibiotics, fluids, and other supportive care as medically indicated.
- **Internal organ hemorrhage:** Patients treated with lifileucel (Amtagvi) may exhibit internal organ hemorrhage. Intraabdominal and intracranial hemorrhage can be life-threatening and have been associated with at least two deaths in patients who received lifileucel (Amtagvi). Withhold or discontinue treatment if internal organ hemorrhage is indicated, or patient is deemed ineligible for IL-2 (aldesleukin) infusion. Patients with persistent or repeated thrombocytopenia after receiving lifileucel (Amtagvi) should not use anticoagulants or must be under close monitoring if the patient must take anticoagulants.
- **Cardiopulmonary:** Patients treated with lifileucel (Amtagvi) may exhibit cardiac disorder. Grade 3 or higher cardiac disorders related to the treatment regimen occurred in 9% (14/156) of patients including tachycardia, atrial fibrillation, arrhythmia, acute myocardial infarction, cardiac ventricular thrombosis, cardiomyopathy, and QT-prolongation. Cardiac arrhythmia resulted in one death among melanoma patients who received treatment. Monitor patients with signs and symptoms of cardiac disorder before and after lifileucel (Amtagvi) infusion. Withhold or discontinue the infusion, if severe

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

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

Contraindications

- None

Precautions/Warnings

- **Hypersensitivity reactions:** Allergic reactions including serious hypersensitivity (e.g., anaphylaxis) may occur with the lifileucel (Amtagvi) infusion. Acute infusion reactions (defined as occurring within 1 day of infusion) may occur and include fever, rigors or chills, tachycardia, rash, hypotension, dyspnea, cough, chest tightness, and wheezing. These events generally resolve on the same day of infusion. Patients should be monitored during and after infusion for signs and symptoms of a severe reaction and treated promptly.

BILLING/CODING INFORMATION:

HCPCS Coding

J9999	Not otherwise classified, antineoplastic drugs

ICD-10 Diagnoses Codes That Support Medical Necessity

C43.0	Malignant melanoma of lip
C43.10 – C43.122	Malignant melanoma of eyelid, including canthus
C43.20 – C43.22	Malignant melanoma of ear and external auricular canal
C43.30 – C43.39	Malignant melanoma of other and unspecified parts of face
C43.4	Malignant melanoma of scalp and neck
C43.51 – C43.59	Malignant melanoma of trunk
C43.60 – C43.62	Malignant melanoma of upper limb, including shoulder
C43.70 – C43.72	Malignant melanoma of lower limb, including hip
C43.8	Malignant melanoma of overlapping sites of skin
C43.9	Malignant melanoma of skin, unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

1. Amtagvi (lifileucel) [package insert]. Iovance Biotherapeutics Manufacturing, LLC. Philadelphia (PA): September 2025.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2026. URL www.clinicalpharmacilogy-ip.com Accessed 02/25/26.
3. DynaMed [database online]. Ipswich, MA: EBSCO Information Services.; 2026. URL http://www.dynamed.com. Accessed 02/27/24.
4. Micromedex Healthcare Series [Internet Database]. Greenwood Village, CO: Thomson Healthcare. Updated periodically. Accessed 02/25/26.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 03/11/26.

GUIDELINE UPDATE INFORMATION:

04/01/24	New Medical Coverage Guideline – Lifileucel (Amtagvi) for the treatment of unresectable or metastatic melanoma in patients previously treated with an immune checkpoint inhibitor or, if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.
09/15/24	Update to the position statement to clarify the IL-2 (aldesleukin) dosing of 600,000 IU/kg intravenously for a maximum of 6 total doses within 4 days after the lifileucel (Amtagvi) infusion.
04/15/25	Review of the guideline to revise the position statement to include specific hematologic parameters and exclusion criteria for lifileucel (Amtagvi) therapy and updating billing and references.

07/15/25	Review of the guideline to revise the position statement to allow for concomitant systemic corticosteroid for the treatment of life-threatening conditions (e.g., adrenal insufficiency).
04/15/26	Review and revision of the guideline consisting of updating the position statement to require a trial of an immune checkpoint inhibitor for BRAF V600 mutation positive disease and updating references.