lifileucel suspension (Amtagvi™)

Medicare Advantage Medical Policy #MNG-066
Original Effective Date: 02/01/2025
Current Effective Date: 02/01/2025

Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Health Plan may consider the use of lifileucel suspension (Amtagvi™)‡ for the treatment of unresectable or metastatic melanoma to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for lifileucel suspension (Amtagvi) will be considered when the following criteria are met:

- Patient is ≥ 18 years of age; AND
- Patient has a diagnosis of unresectable or metastatic melanoma; AND
- Patient has been treated with a programmed death receptor-1 (PD-1) blocking antibody or a programmed death-ligand 1 (PD-L1) blocking antibody. Examples of PD-1/PD-L1 blocking antibodies include pembrolizumab (Keytruda®)‡, nivolumab (Opdivo®)‡, and atezolizumab (Tecentriq®)‡; AND
- If the disease is BRAF V600 mutation positive, the patient has been treated with a BRAF inhibitor with or without a MEK inhibitor. Examples of BRAF inhibitors include encorafenib (Braftovi®)‡, vemurafenib (Zelboraf®)‡, and dabrafenib (Tafinlar®)‡; AND
- Patient has NOT been previously treated with Amtagvi; AND
- Patient has at least one resectable lesion (or aggregate of lesions resected) of a minimum 1.5 cm in diameter post-resection to generate tumor infiltrating leukocyte (TIL) therapy; AND
- Patient has an Eastern Cooperative Oncology Group (ECOG) status score of 0 or 1; AND
- Patient does NOT have any of the following:
    - Uncontrolled brain metastases; OR
    - Organ allograft or prior cell transfer; OR
    - Melanoma of uveal or ocular origin; OR
    - Systemic steroid therapy for any reason; OR
    - Grade 2 or higher hemorrhage within 14 days prior to tumor resection; OR
    - Left Ventricular Ejection Fraction (LVEF) < 45%; OR
    - New York Heart Association (NYHA) heart failure classification greater than 1; OR
    - Forced Expiratory Volume in 1 second (FEV_1) ≤ 60%

When Services Are Considered Not Medically Necessary

Based on review of available data, the Health Plan considers the use of lifileucel suspension (Amtagvi) when the patient has been previously treated with Amtagvi, does NOT have a minimum of 1.5 cm of lesion available for resection, or has an ECOG score > 1 to be **not medically necessary.****

Based on review of available data, the Health Plan considers the use of lifileucel suspension (Amtagvi) when the patient has ANY of the following to be **not medically necessary.****

- Uncontrolled brain metastases; OR
- Organ allograft or prior cell transfer; OR
- Melanoma of uveal or ocular origin; OR
- Systemic steroid therapy for any reason; OR
- Grade 2 or higher hemorrhage within 14 days prior to tumor resection; OR
- Left Ventricular Ejection Fraction (LVEF) < 45%; OR
- New York Heart Association (NYHA) heart failure classification greater than 1; OR
- Forced Expiratory Volume in 1 second (FEV_1) $\leq$ 60%

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers the use of lifileucel (Amtagvi) when the patient selection criteria are not met (except those denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Amtagvi is a tumor-derived autologous T cell immunotherapy indicated for the treatment of unresectable or metastatic melanoma in adults who have been previously treated with a programmed death receptor-1 (PD-1) blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor. It is manufactured from resected patient tumor tissue from one or more tumor lesions and is composed primarily of T cells of the CD4+ and CD8+ T cell lineages. Prior to infusion, the patient should be treated with lymphodepleting chemotherapy consisting of cyclophosphamide followed by fludarabine. Amtagvi is administered between 24 hours and 4 days after completion of lymphodepleting chemotherapy. After completion of the Amtagvi infusion, IV interleukin-2 (IL-2), given as Proleukin®‡ (aldesleukin IV infusion) is administered for up to 6 doses (dosed every 8-12 hours) to support cell expansion *in vivo*. Treatment must occur at a treatment center certified by the manufacturer. There are boxed warnings in the label for this product for treatment-related mortality, prolonged severe cytopenia, cardiac disorders, respiratory failure, and acute renal failure.

Melanoma is a relatively common cancer in the U.S. with an estimated 100,640 new cases predicted each year. Invasive melanoma is only approximately 1% of these skin cancers, but it results in the most death. Risk factors for melanoma include sun exposure, male sex, high nevus count, atypical nevi, family and/or personal history, and others. Current primary treatment options for melanoma that has metastasized or cannot be surgically treated include immunotherapy using immune checkpoint inhibitors (such as anti-PD-1/PD-L1 agents) or targeted therapy involving BRAF/MEK inhibitors, particularly if the melanoma carries a BRAF V600 mutation. For patients who do not respond to or experience a relapse after receiving immunotherapy or targeted therapy, alternative immunotherapies or targeted therapies with different mechanisms of action can be considered. In cases of continued disease progression, chemotherapy is an option, but its efficacy is limited, with response rates reported at only 4 to 12% and a relatively short median overall survival rate of 7 months. Amtagvi is the first treatment to be approved for these patients who have progressive disease after immunotherapy and targeted therapy. The National Comprehensive Cancer Network (NCCN) guidelines for cutaneous melanoma (Version 2.2024) recommend consideration of TIL therapy for patients with good performance status who have progressed on anti-PD-1 based therapy and BRAF/MEK inhibition (if BRAF V600 mutation present). These guidelines further state that TIL therapy should not be considered for patients with inadequate cardiac, pulmonary, and/or renal function, poor performance status, or with untreated or active brain metastases.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Amtagvi is a tumor-derived autologous T cell immunotherapy approved 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.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of a single treatment with Amtagvi was evaluated in a global, multicenter, multicohort, open-label, single-arm clinical study. This study enrolled patients with unresectable or metastatic melanoma who had previously been treated with at least one systemic therapy, including a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor or BRAF inhibitor with MEK inhibitor. This study excluded patients 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), left ventricular ejection fraction (LVEF) less than 45% or New York Heart Association (NYHA) functional classification greater than Class 1, and patients with FEV1 of less than or equal to 60%.

Of the 111 patients who underwent tumor resection, 22 (19.8%) did not receive Amtagvi for the following reasons: inability to manufacture Amtagvi (n=6), disease related death (n=3), meeting exclusion criteria (n=5), disease progression (n=3), starting new anti-cancer therapy or consent withdrawal (n=3), or adverse events from lymphodepletion including one death (n=22). Among the 89 patients who received Amtagvi, two were excluded because the product did not meet specification and five were excluded due to product comparability.

The primary efficacy analysis set included 82 patients who received Amtagvi. Among these, nine patients received Amtagvi at a dose less than 7.5×10^9 viable cells and did not achieve an objective response. The recommended Amtagvi dosing range was set at 7.5×10^9 to 72×10^9 viable cells. The median time from tumor tissue procurement to the end of the manufacturing process was 23 days and to infusion was 34 days.

All 73 patients received prior anti-PD-(L)1 therapy, 63 received prior anti-CTLA-4 therapy, 42 received anti-PD1/anti-CTLA-4 combination therapy, and 20 received a BRAF inhibitor or combination therapy with BRAF and MEK inhibitors.

Amtagvi was administered following a lymphodepleting regimen consisting of cyclophosphamide 60 mg/kg daily with mesna for 2 days followed by fludarabine 25 mg/m2 daily for 5 days. Three to 24 hours after 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 *in vivo*. The median administered Amtagvi dose was 21.1×10^9 viable cells. The median number of administered IL-2 doses was 6.

Efficacy was established on the basis of objective response rate (ORR) and duration of response (DoR). The median time to initial response to Amtagvi was 1.5 months. The ORR was 31.5% (95% CI 21.1, 43.4) with a 4.1% complete response and 27.4% partial response. The median DoR was not reached (4.1, NR).

References

1. Amtagvi [package insert]. Iovance Biotherapeutics, Inc. Philadelphia, PA. Updated February 2024.
2. Amtagvi Drug Evaluation. Express Scripts. Updated February 2024.
3. Amtagvi New Drug Review. IPD Analytics. Updated February 2024.
4. The NCCN Melanoma: Cutaneous Clinical Practice Guidelines in Oncology (version 2.2024) © 2024 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org

Policy History

Original Effective Date: 02/01/2025
Current Effective Date: 02/01/2025
11/19/2024 UM Committee review. New policy
Next Scheduled Review Date: 11/2025

Coding

The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of the Health Plan Medical Policy Coverage Guidelines is with the Health Plan and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in the Health Plan Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not
contained herein. Any use of CPT outside of the Health Plan Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	C9399, J9999
ICD-10 Diagnosis	All related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or

diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses

coverage for a specific service, refer to the Medicare Coverage Database at the following link: https://www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.