BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Melanoma Vaccines

Policy #: 604
Category: Medical

Latest Review Date: January 2020
Policy Grade: B

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Effective for dates of service on or after June 15, 2017:
Blue Advantage will treat **Imlygic® (talimogene laherparepvec)** as a **covered benefit** for treatment as a direct intralesional injection into recurrent, unresectable melanoma when any of the following indications are met:

1. Stage III disease in-transit; or
2. Local/satellite recurrence of disease; or
3. In-transit recurrence of disease.

Blue Advantage will treat **Imlygic® (talimogene laherparepvec)** as **investigational** when the above criteria are not met, and for all other indications.

Blue Advantage will treat **melanoma vaccines, with the exception of Imlygic® (talimogene laherparepvec)** as a **non-covered benefit** and as **investigational**.

Effective for dates of service August 22, 2015 through June 14, 2017:
Blue Advantage will treat **melanoma vaccines** as a **non-covered benefit** and as **investigational**.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

Tumor vaccines are a type of active immunotherapy that attempts to stimulate the patient's own immune system to respond to tumor cell antigens. A wide range of vaccine types are available including use of autologous tumor cells, allogeneic tumor cells, and tumor-specific moieties including peptides, gangliosides, and DNA plasmids. A variety of mechanisms appear to exist as possible obstacles to successful active immunotherapy using vaccines. Current areas of investigation include new and different vaccine preparations, as well as various forms of immune modulation to enhance vaccine effectiveness.

Vaccines using crude preparations of tumor material were first studied by Ehrlich over 100 years ago. However, the first modern report to suggest benefit in cancer patients did not appear until 1967. Melanoma has been viewed as a particularly promising target for vaccine treatment because of its immunologic features, which include the prognostic importance of lymphocytic infiltrate at the primary tumor site, the expression of a wide variety of antigens, and the occasional occurrence of spontaneous remissions. Melanoma vaccines can be generally categorized or prepared in the following ways:

- **Whole-cell vaccines** prepared using melanoma cells or crude subcellular fractions of melanoma cell lines
    - **Autologous whole-cell vaccines** in which tumor cells are harvested from the tissue of excised cancers, irradiated, and potentially modified with antigenic molecules to increase immunogenicity and made into patient-specific vaccines (e.g., M-Vax®, AVAX Technologies)
    - **Autologous heat-shock protein-peptide complexes vaccines** in which a patient's tumor cells are exposed to high temperatures and then purified to make patient-specific vaccines (e.g., Oncophage®, Antigenics Inc.), and
    - **Allogeneic whole-cell vaccines** in which intact or modified allogeneic tumor cell lines from other patients are lysed by mechanical disruption or viral infection and used to prepare vaccine (e.g., Canvaxin®, CancerVax Corp.; or Melacine®, University of Southern California).
- **Dendritic cell vaccines** in which autologous dendritic cells are pulsed with tumor-derived peptides, tumor lysates, or antigen encoding RNA or DNA to produce immunologically enhanced vaccines.
- **Peptide vaccines** consisting of short, immunogenic peptide fragments of proteins (e.g., melanoma antigen E [MAGE]; B melanoma antigen [BAGE]) used alone or in different combinations to create vaccines of varying antigenic diversity, depending on the peptide mix.
- **Ganglioside vaccines** in which glycolipids present in cell membranes are combined with an immune adjuvant (e.g., GM2) to create vaccines.
- **DNA vaccines** created from naked DNA expression plasmids.
- **Viral vectors** in which DNA sequences are inserted into attenuated viruses for gene delivery to patient immune systems.
- **Anti-idiotype vaccines** made from monoclonal antibodies with specificity for tumor antigen-reactive antibodies.

KEY POINTS:

Summary of Evidence

The evidence for melanoma vaccines in patients who have stage II-IV melanoma includes studies on the use of new and different vaccine preparations, as well as on various forms of immune-modulation as potential techniques for enhancing vaccine effectiveness. Relevant outcomes include overall survival, disease-specific survival, and morbid events. Despite considerable activity in numerous studies over the past 20 years, no melanoma vaccine has received U.S. Food and Drug Administration marketing approval. One randomized controlled trial (RCT) of a gp100 melanoma vaccine has reported a significant increase in response rate and progression-free survival. However, several other RCTs have reported no improvements in disease-free survival or overall survival rates with the use of study vaccines. Additionally, other RCTs were closed early due to inferiority of results with study vaccines. Other phase 3 RCTs are underway or in the planning stages to further investigate vaccine preparations to treat malignant melanoma. For use of melanoma vaccines for treatment of patients with stage II-IV melanoma, the body of evidence is insufficient to conclude that anti–melanoma vaccines of any type, alone or in combination with immunomodulating agents, significantly improve survival outcomes

compared with non–vaccine therapies. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements
The National Comprehensive Cancer Network® (NCCN) 2019 Clinical Practice Guidelines® for melanoma contain a Category 1 recommendation for intralesional treatment of melanoma with T-VEC for stage III disease or local, satellite, and/or in-transit recurrence.

U.S. Preventive Services Task Force Recommendations
Not applicable.

KEY WORDS:
Melanoma vaccine, tumor vaccine, active immunotherapy, M-Vax®, Oncophage®, Canvaxin®, Melacine®, Imlygic®, talimogene laherparepvec

APPROVED BY GOVERNING BODIES:
On October 27, 2015 the FDA approved Amgen, Inc.'s talimogene laherparepvec (Imlygic, Thousand Oaks, CA), the first oncolytic virus therapy for the treatment of melanoma lesions in the skin and lymph nodes.

BENEFIT APPLICATION:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:
CPT Codes:

86849	Unlisted immunology procedure
J9325	Injection, talimogene laherparepvec, per 1 million plaque forming units

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POLICY HISTORY:

Medical Policy Group, July 2015
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Medical Policy Group, June 2016
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Medical Policy Group, June 2017
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