I. POLICY

Talimogene laherparepvec (Imlygic™) is considered medically necessary for unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery in individuals ≥ 18 years old who are not pregnant or immunocompromised.

Note: Conditions indicative of an individual being immunocompromised include those with a history of primary or acquired immunodeficient states, leukemia, lymphoma, AIDS or other clinical manifestations of infection with human immunodeficiency viruses, and those on immunosuppressive therapy.

Talimogene laherparepvec treatment has not been shown to have an effect on visceral metastases or improve overall survival.

The safety and efficacy of talimogene laherparepvec have not been established in pediatric patients.

Cross-reference:
- MP 2.187 Treatment of Cancer Using Human PD-1 Receptor Blocking Antibodies
- MP 2.161 Ipilimumab (Yervoy™)
- MP-2.103 Off-Label Use of Medications

II. PRODUCT VARIATIONS

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.
MEDICAL POLICY

<table>
<thead>
<tr>
<th>POLICY TITLE</th>
<th>TALIMOGENE LAHERPAREPVEC (IMLYGIC™)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POLICY NUMBER</td>
<td>MP-2.340</td>
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</table>

FEP PPO*


Note for Medicare Advantage:
FDA approved drugs used for indications other than what is indicated on the FDA approved product label may be covered under Medicare if it is determined that the use is medically accepted, taking into consideration the Medicare recognized national drug compendia, authoritative medical literature and/or accepted standards of medical practice. Refer to Medicare Benefit Policy Manual (100-2, Chapter 15, Section 50.4.2- Unlabeled Use of Drug). http://www.cms.gov/manuals/Downloads/bp102c15.pdf

III. DESCRIPTION/BACKGROUND

On October 27, 2015 the U.S. Food and Drug Administration (FDA) approved the Biologics License Application for Imlygic™ (talimogene laherparepvec), a genetically modified oncolytic viral therapy indicated for the local treatment of unresectable cutaneous, subcutaneous and nodal lesions in patients with melanoma recurrent after initial surgery. Imlygic has not been shown to improve overall survival or have an effect on visceral metastases. Imlygic is the first oncolytic viral therapy approved by the FDA based on therapeutic benefit demonstrated in a pivotal study

Imlygic is a genetically modified herpes simplex virus type 1 injected directly into tumors where it replicates inside tumors and produces GM-CSF, an immunostimulatory protein. Imlygic then causes the tumor to rupture and die in a process called lysis. The rupture of the tumor causes the release of tumor-derived antigens, which together with virally-derived GM-CSF may promote an anti-tumor immune response. However, the exact mechanism of action is unknown and being further investigated.

Dosing and Administration

For intralesional injection only. Do not administer intravenously.

Administer Talimogene laherparepvec (Imlygic™) by injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance.

- Administer Talimogene laherparepvec (Imlygic™) by injection into cutaneous, subcutaneous, and/or nodal lesions.
- Recommended starting dose is up to a maximum of 4 mL of talimogene laherparepvec (Imlygic™) at a concentration of 106 (1 million) plaque-forming units (PFU) per mL. Subsequent doses should be administered up to 4 mL of talimogene laherparepvec (Imlygic™) at a concentration of 108 (100 million) PFU per mL.
See full prescribing information for complete dosing and administration recommendations. Continue talimogene laherparepvec (Imlygic™) treatment for at least 6 months unless other treatment is required or until there are no injectable lesions to treat.

IV. RATIONALE

The safety and efficacy of intrallesional injections of Imlygic compared with subcutaneously administered GM-CSF was evaluated in a multicenter, open-label, randomized clinical study in patients with stage IIIB, IIIC, and IV melanoma that was considered to be not surgically resectable. Imlygic was injected into cutaneous, subcutaneous, or nodal melanoma lesions and was not injected into visceral lesions. Previous systemic treatment for melanoma was allowed. Patients with active cerebral metastases, bony metastases, extensive visceral disease, primary ocular or mucosal melanoma, evidence of immunosuppression, or receiving treatment with a systemic antiherpetic agent were excluded from the study.

The study included 250 (57%) men and 186 (43%) women. The mean age was 63 (range: 22 to 94) years. Most patients (98%) were white. Seventy percent (70%) of patients had baseline Eastern Cooperative Oncology Group (ECOG) performance status of zero. Seventy percent (70%) of patients had stage IV disease (27% M1a; 21% M1b; and 22% M1c), and 30% had stage III disease. Fifty-three percent (53%) of patients had received prior therapy for melanoma (other than or in addition to surgery, adjuvant therapy, or radiation), and 58% were seropositive for wild-type HSV-1 at baseline.

A total of 436 patients were randomized to receive either Imlygic (n = 295) or GM-CSF (n = 141). Imlygic was administered by intrallesional injection at an initial concentration of 106 (1 million) PFU per mL on Day 1, followed by a concentration of 108 (100 million) PFU per mL on Day 21 and every 2 weeks thereafter, at a dose of up to 4 mL per visit. GM-CSF was administered subcutaneously in 28-day cycles, i.e., 125 μg/m² daily for 14 days followed by 14 days without GM-CSF administration.

Patients were to be treated for at least 6 months or until there were no injectable lesions. During this period, treatment could continue despite an increase in size in existing lesion(s) and/or development of new lesion(s), unless the patient developed intolerable toxicity or the investigator believed that it was in the best interest of the patient to stop treatment or to be given other therapy for melanoma. After 6 months of treatment, patients were to continue treatment until clinically relevant disease progression (i.e., disease progression associated with a decline in performance status and/or alternative therapy was required in the opinion of the investigator), up to 12 months. Patients experiencing a response at 12 months after the start of treatment could continue treatment for up to an additional 6 months, unless there were no remaining injectable lesions or disease progression. All patients were to be followed for survival status for at least 36 months.
The major efficacy outcome was durable response rate (DRR), defined as the percent of patients with complete response (CR) or partial response (PR) maintained continuously for a minimum of 6 months. Tumor responses were determined according to World Health Organization (WHO) response criteria modified to allow patients who developed new lesions or disease progression of existing lesions to continue the treatment and be evaluated later for tumor response.

The DRR was 16.3% in the Imlygic arm and 2.1% in the GM-CSF arm in the overall study population. The unadjusted relative risk was 7.6 (95% CI: 2.4, 24.1), with a p-value < 0.0001. The median time to response was 4.1 (range: 1.2 to 16.7) months in the Imlygic arm. There was no statistically significant difference in overall survival (OS) between the Imlygic and the GM-CSF arms. The median OS in the overall study population was 22.9 months in the Imlygic arm and 19.0 months in the GM-CSF arm (p = 0.116).

V. DEFINITIONS
NA

VI. BENEFIT VARIATIONS
The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER
Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION
Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the
MEDICAL POLICY

POLICY TITLE TALIMogene LAHERParepvec (IMLyGIC™)
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terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>J9325</td>
<td>Injection, talimogene laherparepvec, per 1 million plaque forming units</td>
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<table>
<thead>
<tr>
<th>ICD-10-CM Diagnosis Codes</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>C43.0</td>
<td>Malignant melanoma of lip</td>
</tr>
<tr>
<td>C43.11</td>
<td>Malignant melanoma of right eyelid, including canthus</td>
</tr>
<tr>
<td>C43.12</td>
<td>Malignant melanoma of left eyelid, including canthus</td>
</tr>
<tr>
<td>C43.21</td>
<td>Malignant melanoma of right ear and external auricular canal</td>
</tr>
<tr>
<td>C43.22</td>
<td>Malignant melanoma of left ear and external auricular canal</td>
</tr>
<tr>
<td>C43.31</td>
<td>Malignant melanoma of nose</td>
</tr>
<tr>
<td>C43.39</td>
<td>Malignant melanoma of other parts of face</td>
</tr>
<tr>
<td>C43.4</td>
<td>Malignant melanoma of scalp and neck</td>
</tr>
<tr>
<td>C43.51</td>
<td>Malignant melanoma of anal skin</td>
</tr>
<tr>
<td>C43.52</td>
<td>Malignant melanoma of skin of breast</td>
</tr>
<tr>
<td>C43.59</td>
<td>Malignant melanoma of other part of trunk</td>
</tr>
<tr>
<td>C43.61</td>
<td>Malignant melanoma of right upper limb, including shoulder</td>
</tr>
<tr>
<td>C43.62</td>
<td>Malignant melanoma of left upper limb, including shoulder</td>
</tr>
<tr>
<td>C43.71</td>
<td>Malignant melanoma of right lower limb, including hip</td>
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<tr>
<td>C43.72</td>
<td>Malignant melanoma of left lower limb, including hip</td>
</tr>
<tr>
<td>C43.8</td>
<td>Malignant melanoma of overlapping sites of skin</td>
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<tr>
<td>Z51.11</td>
<td>Encounter for antineoplastic chemotherapy</td>
</tr>
<tr>
<td>Z51.12</td>
<td>Encounter for antineoplastic immunotherapy</td>
</tr>
</tbody>
</table>

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

IX. REFERENCES


MEDICAL POLICY

POLICY TITLE | TALIMOGENE LAHERPAREPVEC (IMLYGIC™)

POLICY NUMBER | MP-2.340

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Talimogene laherparepvec: Drug information. Lexicomp®


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X. POLICY HISTORY

| Administrative Update 11/22/16 | Variation section reformatted.
| Administrative Update 1/1/17 | Added new code J9325 and removed end dated code C9472 as well as NOC code J3590; effective 1/1/17.

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