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Medication Policy Manual

Policy No: dru238

Topic: Yervoy®, ipilimumab

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IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Ipilimumab (Yervoy) is an intravenous immune therapy medication used in the treatment of advanced melanoma.

Policy/Criteria

I. Most contracts require prior authorization approval of ipilimumab (Yervoy) prior to coverage. Ipilimumab (Yervoy) may be considered medically necessary when criteria A or B are met:

A. A diagnosis of **unresectable (stage III) or metastatic (stage IV) melanoma** AND ipilimumab (Yervoy) will be used in one of two treatment settings described below in criteria 1. or 2.:

1. Ipilimumab (Yervoy) will be used as monotherapy.

OR

2. Ipilimumab (Yervoy) will be used in combination with nivolumab (Opdivo) AND both a. and b. below are met:

a. No prior use of a programmed death receptor-1 blocking antibody therapy (PD-1 inhibitor) (See *Appendix 1*).

AND

b. Ipilimumab (Yervoy) will be used along with nivolumab (Opdivo) for a maximum of four doses.

OR

B. A diagnosis of **resectable cutaneous melanoma** when criteria 1. through 4. below are met:

1. Documentation of pathologic involvement of regional lymph nodes (stage III).

AND

2. Ipilimumab (Yervoy) is used as adjuvant treatment

AND

3. No prior use of a programmed death receptor-1 blocking antibody therapy (PD-1 inhibitor) (See *Appendix 1*).

AND

4. Ipilimumab (Yervoy) will be used as monotherapy

II. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services does not consider ipilimumab (Yervoy) to be a self-administered medication.

B. When prior authorization is approved, ipilimumab (Yervoy) may be authorized as follows:

1. **Unresectable or metastatic melanoma:** one-time for a maximum of 4 infusions (one treatment course) of up to 3 mg/kg/dose [up to 600 billing units per claim (600 mg)].

2. **Adjuvant setting:** up to 10 mg/kg every 3 weeks for four doses then up to 10 mg/kg every twelve weeks for up to 3 years.

C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Ipilimumab (Yervoy) is considered investigational when:

A. Infused for more than a total of 4 doses (one treatment course) in unresectable or metastatic melanoma

B. Used in combination with other anticancer medications, including but not limited to dabrafenib (Tafinlar), pembrolizumab (Keytruda) trametinib (Mekinist), or vemurafenib (Zelboraf) (See *Appendices 2 and 3*).

C. Used for all other conditions, including but not limited to:

1. Breast cancer

2. Cervical cancer

3. Kidney cancer

4. Leukemia

5. Lung cancer

6. Non-Hodgkin's lymphoma

7. Non-small cell lung cancer

8. Ovarian cancer

9. Pancreatic cancer

10. Prostate cancer

11. Renal cell cancer

12. Sarcoma

13. Urothelial cancer

Position Statement

- Ipilimumab (Yervoy) is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody which is used in the treatment of melanoma.
- Ipilimumab (Yervoy) may be covered for treatment of malignant melanoma that is unresectable or has metastasized to other areas, a setting where it has been shown to improve overall survival relative to supportive care.
- Ipilimumab (Yervoy) may be covered for up to four doses, the dosing at which it has been shown to be safe and effective.
- The risk versus the potential benefit of high-dose ipilimumab (Yervoy) as an adjuvant therapy for resectable cutaneous melanoma with pathologic involvement of regional lymph nodes (stage III) is unclear. This regimen is poorly tolerated and it is not known if the toxicities of this therapy outweigh potential clinical benefit on overall survival.
- There is no evidence that it is effective in treating other types of cancer.
- Ipilimumab (Yervoy) has been associated with severe and life-threatening immune-mediated adverse reactions. Healthcare providers should be aware of these risks and provide appropriate management for adverse reactions.

Clinical Efficacy

USE AS MONOTHERAPY FOR ADVANCED MELANOMA

- A large study evaluated the effects of ipilimumab (Yervoy) on overall survival (OS) in patients with previously treated, unresectable or metastatic melanoma. [1]
    - The triple-arm study included 676 patients with unresectable or metastatic melanoma who had received one or more prior treatments.
    - The study compared ipilimumab (Yervoy) with a gp100 peptide vaccine (an experimental immunotherapy used in the treatment of melanoma). gp100 peptide vaccine has not been shown to impact OS in this population.
    - Ipilimumab (Yervoy) was administered in a dose of 3 mg/kg intravenously (IV) every three weeks for a total of 4 doses (one treatment course).
    - Patients in the study who received ipilimumab (Yervoy) had a median OS of approximately 10 months, compared with a reported median OS of 6.4 months in the vaccine-only arm. This is considered a clinically relevant improvement in OS.
    - Limitations to the study included uncertain blinding and concealment of allocation, and uncertainty as to whether the comparator (peptide vaccine) had any positive or negative impact on study patients.
- Ipilimumab (Yervoy) has not been compared with any other therapy for unresectable or metastatic melanoma in patients who have had prior medication therapy for melanoma. [2]
- A second study compared ipilimumab (Yervoy) plus dacarbazine versus dacarbazine alone in patients with unresectable or metastatic melanoma who had no prior medication therapy. [3]
    - The study reported a median OS advantage of approximately 2 months in the ipilimumab (Yervoy) treatment arm.
    - There is low confidence in the results from the trial because of a very high proportion of missing data (~35%) and the potential for confounding due to additional therapies that were used after disease progression. [10,11]

USE IN COMBINATION WITH NIVOLUMAB (OPDIVO) FOR ADVANCED MELANOMA

- The use of ipilimumab (Yervoy) in combination with nivolumab (Opdivo) was studied in one randomized, double-blind, triple-arm study included 945 patients with unresectable or metastatic melanoma. [10]
    - Patients had not received prior systemic therapy for advanced disease, such as ipilimumab (Yervoy) or a programmed death-1 (PD-1) inhibitor [nivolumab (Opdivo), or pembrolizumab (Keytruda)].
    - Patients were treated with ipilimumab (Yervoy) 3 mg/kg IV along with nivolumab (Opdivo) 1 mg/kg IV every three weeks for four doses, followed by nivolumab (Opdivo) 3 mg/kg IV every two weeks, until disease progression.
    - Combination therapy improved median PFS by approximately 8.5 months relative to monotherapy with either ipilimumab (Yervoy) or nivolumab (Opdivo) [11.5 months versus 2.9 months or 6.9 months, respectively]. The OS data was not yet mature at the time this trial was published.

- Ipilimumab (Yervoy) has not been studied in combination with pembrolizumab (Keytruda), another PD-1 inhibitor.

USE AS AN ADJUVANT THERAPY FOR CUTANEOUS MELANOMA

- A large, randomized, double-blind, trial evaluated ipilimumab (Yervoy) as an adjuvant therapy in subjects with stage III, resectable cutaneous melanoma. [12,13]
    * Subjects were diagnosed with histologically confirmed cutaneous melanoma that was metastatic to the lymph nodes only, and had complete excision of the cutaneous lesion with good margins and a complete regional lymphadenectomy. Ipilimumab (Yervoy) 10 mg/kg (high-does) was compared with placebo, each given IV every three weeks for four doses, then every three months for a maximum of three years.
    * At a medium follow-up of 2.7 years, recurrence-free survival (RFS), the primary endpoint, was improved in the ipilimumab (Yervoy) therapy arm relative to placebo (26 months versus 17 months, respectively).
    * In an updated analysis, at a medium follow-up of 5.3 years, the rate of OS was 65.4% in the ipilimumab (Yervoy) group, as compared to 54.4% in the placebo group (hazard ratio for death, 0.72; 95.1% CI, 0.58 to 0.88; P = 0.001).
    * More than half of the subjects withdrew from the ipilimumab (Yervoy) treatment arm due to adverse events versus only 4% in the placebo arm. Immune-related adverse events of any grade occurred in 90% of patients in the ipilimumab group and 40% of patients in the placebo group. Immune-related adverse events of grade 3 to 5 occurred in 43% of patients in the ipilimumab treatment group and in 3% of patients in the placebo group. Additionally, five patients in the ipilimumab (Yervoy) arm died due to immune-mediated adverse events attributed to treatment.
- Despite FDA approval, the small change in OS, high toxicity, and poor tolerability of high-dose ipilimumab (Yervoy) observed in this study, it is unclear if the harms of this therapy outweigh any potential clinical benefit when it is used as an adjuvant therapy after complete resection of cutaneous melanoma and regional lymphadenectomy due to pathologic involvement of regional lymph nodes. In addition, there are no studies demonstrating the efficacy of ipilimumab (Yervoy) when used at a lower dose in the adjuvant setting, or whether a potential clinical benefit at a lower dose will outweigh toxicities.

CLINICAL GUIDELINES

- The National Comprehensive Cancer Network (NCCN) melanoma guideline lists ipilimumab (Yervoy) as a category 1 recommendation as a second-line or subsequent therapy in patients with or without BRAF V600 mutation positive melanoma. The use of ipilimumab (Yervoy) in combination with nivolumab (Opdivo) is a category 2A recommendation in the first-line metastatic setting. [4]
- The NCCN gives high-dose ipilimumab (Yervoy) a category 1 recommendation in the adjuvant treatment of stage III cutaneous melanoma. [4]

- Although the NCCN melanoma guideline includes a footnote indicating that re-induction with ipilimumab (Yervoy) may be considered for select patients who experienced no significant systemic toxicity during prior therapy and who relapse after initial clinical response or progress after stable disease, the safety and efficacy of additional infusions of ipilimumab (Yervoy) beyond a total of 4 doses (one treatment course) is unknown. There are no clinical trials or data to support this. Therefore, while the NCCN recognizes the use of additional doses of ipilimumab (Yervoy) as a category 1 recommendation, there is insufficient evidence to support additional doses beyond four for metastatic melanoma and, therefore, the use of additional doses is considered investigational. [1,4,5]
    * The pivotal clinical trial evaluated ipilimumab (Yervoy) administered in a dose of 3 mg/kg IV every 3 weeks for a total of four infusions (one treatment course).
    * Although 40 (5.9%) of the 676 subjects enrolled in the study went on to receive an additional treatment course of ipilimumab (Yervoy) after disease progression, only six (15%) achieved best overall response (complete response plus partial response). In addition, a majority (~73%) of the re-treated patients also received concomitant gp100 peptide vaccine. [5]
    * Current evidence is not sufficient to establish the safety and effectiveness of a second treatment course of ipilimumab (Yervoy) in advanced melanoma. [1,5]

INVESTIGATIONAL USES

- Data to support the use of combination treatment with ipilimumab (Yervoy) and pembrolizumab (Opdivo) for the treatment of small cell lung cancer (SCLC) is limited to a single phase I/II trial. Response rates were reported with the combination treatment in SCLC after primary therapy, but not overall survival. Combination treatment with ipilimumab (Yervoy) and pembrolizumab (Opdivo) have not been shown to be superior to many available alternative therapies in patients with SCLC. Larger, well-designed, randomized, controlled trials are needed to confirm preliminary results. [14]
- Ipilimumab (Yervoy) demonstrated some antitumor activity in small trials in patients with non-Hodgkin's Lymphoma, prostate cancer, lung cancer, sarcoma, and renal cell cancer. Larger, well-controlled clinical trials in these settings are needed to confirm clinical benefit. [6, 7. 8]

Regence Pharmacy Services performs independent analyses of oncology medications. The Regence Pharmacy Services analysis and coverage policy may differ from NCCN guidelines.

Safety [2]

- The most common adverse effects (AEs) reported with ipilimumab (Yervoy) include fatigue, diarrhea, pruritus, rash, and colitis. Additional common AEs observed at the higher, 10 mg/kg dose, include nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia.

- Ipilimumab (Yervoy) carries a boxed warning for severe immune-mediated adverse reactions including immune-mediated hepatitis and endocrinopathies. For severe reactions, the prescribing information recommends ipilimumab (Yervoy) be permanently discontinued. For moderate reactions, the prescribing information states the dose of ipilimumab (Yervoy) should not be given and systemic corticosteroids are recommended.
- Liver function tests, thyroid function tests, and clinical chemistries should be evaluated prior to each dose of ipilimumab (Yervoy). Hormone replacement therapy should be initiated as needed.

Dosing Considerations [2]

- For unresectable and metastatic melanoma, ipilimumab (Yervoy) is given as an IV infusion over 90 minutes at a dose of 3 mg/kg. It is given once every 3 weeks for a total of 4 doses (one treatment course). The safety and efficacy of additional doses has not been established.
- The dosing of ipilimumab (Yervoy) in combination with nivolumab (Opdivo) is also 3 mg/kg IV every three weeks for a maximum of four doses.
- High-dose (10 mg/kg IV every three weeks) ipilimumab (Yervoy), which is approved for adjuvant use in patients with stage III melanoma, is poorly tolerated. In a phase 3 trial in this setting, over half (52%) of subjects in the ipilimumab (Yervoy) treatment arm discontinued therapy due to an AE versus only 4% of subjects in the placebo arm. [12]
- A study is currently underway (ECOG 1609), which evaluates adjuvant ipilimumab 3 mg or 10 mg/kg versus high-dose interferon alfa for resected high-risk melanoma. Results are not yet available.
- Therefore, there is insufficient evidence demonstrating the efficacy or tolerability of ipilimumab (Yervoy) when used at a lower dose in the adjuvant setting, or whether a potential clinical benefit at a lower dose will outweigh toxicities.

Appendix 1: Examples of programmed death receptor-1 (PD-1) blocking monoclonal antibodies [a]
atezolizumab (Tecentriq®)
avelumab (Bavencio®)
nivolumab (Opdivo®)
pembrolizumab (Keytruda®)

[a] Several PD-1s are in the drug development pipeline. This is a list of the PD-1 inhibitors FDA-approved in the US at the time this policy was approved.

Appendix 2: Immunotherapies Used in the Treatment of Melanoma [2]
aldesleukin (IL-2; Proleukin®)
ipilimumab (Yervoy®)
nivolumab (Opdivo®)
pembrolizumab (Keytruda®)

Appendix 3: Targeted therapies Used in the Treatment of Melanoma [2]
cobimetinib (Cotellic™)
dabrafenib (Tafinlar®)
trametinib (Mekinist®)
vemurafenib (Zelboraf®)

Cross References
BRAF Gene Mutation Testing To Select Melanoma Patients for BRAF Inhibitor Targeted Therapy, Medical Policy Manual, Policy No. 41
Cotellic™, cobimetinib, Medication Policy Manual, Policy No. 442
Imlygic™, talimogene laherparepvec, Medication Policy Manual, Policy No. 445
Keytruda®, pembrolizumab, Medication Policy Manual, Policy No. 367
Mekinist™, trametinib, Medication Policy Manual, Policy No. 307
Opdivo®, nivolumab, Medication Policy Manual, Policy No. 390
Tafinlar®, dabrafenib, Medication Policy Manual, Policy No. 308
Zelboraf™, vemurafenib, Medication Policy Manual, Policy No. 266

Codes	Number	Description
HCPCS	J9228	Injection, ipilimumab, 1 mg
ICD-10	C43.0, C43.10-C43.12, C43.20-C43.22, C43.30, C43.31, C43.39, C43.4, C43.51, C43.52, C43.59-C43.62, C43.70-C43.72, C43.8, C43.9, C69.90-C69.92, C79.31, C80.0, C80.1, Z85.820	Malignant melanoma

References

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Revision History

Revision Date	Revision Summary
10/13/2017	Added coverage criteria for adjuvant use in resectable cutaneous melanoma when there is pathologic involvement of regional lymph nodes (stage III).
5/13/2016	Added adjuvant use of high-dose (10 mg/kg) ipilimumab (Yervoy) for resectable cutaneous melanoma when there is pathologic regional lymph node involvement as not medically necessary. This is a newly approved FDA-labeled use. Updated guideline recommendations, added newly published evidence, and updated Appendices.
12/11/2015	Added policy coverage criteria for the use in combination with Opdivo. Clarified that dose is 3 mg/kg. Add Appendix 1, with a list of available PD1s Add Appendix 3, with a list of other targeted therapies for melanoma