BACKGROUND

Keytruda, a human programmed death receptor-1 blocking antibody, is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following Yervoy® (ipilimumab intravenous injection) and, if BRAF V600 mutation positive, a BRAF inhibitor (e.g., Tafinlar® [dabrafenib capsules], Zelboraf® [vemurafenib tablets]).

The recommended dose of Keytruda is 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks. Keytruda is available as a preservative-free, white to off-white lyophilized powder containing 50 mg of pembrolizumab in a single-use vial. Each vial is reconstituted with 2.3 mL of Sterile Water for Injection (resulting concentration 25 mg/mL) and then diluted with 0.9% Sodium Chloride Injection for intravenous infusion to a final concentration of between 1 mg/mL to 10 mg/mL.

REQUIRED REVIEW AND APPROVALS

This policy involves the use of Keytruda. Prior authorization is recommended for medical benefit coverage of Keytruda. Approval is recommended for those who meet the conditions of coverage in the Criteria, Dosing, Initial/Extended Approval, Duration of Therapy, and Labs/Diagnostics for the diagnosis provided. The requirement that the patient meet the Criteria for coverage of the requested medication applies to the initial authorization only. Waste Management applies for all covered conditions. Conditions Not Recommended for Approval are listed following the recommended authorization criteria and Waste Management section. Requests for uses not listed in this policy will be reviewed for evidence of efficacy and for medical necessity on a case-by-case basis.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Keytruda as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Keytruda to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy unless otherwise noted below.
CRITERIA:

Coverage of Keytruda is recommended in those who meet one of the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. Melanoma

Criteria. The patient must meet the following criteria (A AND B):
A. Keytruda is prescribed by or in consultation with an oncologist; AND
B. The patient has unresectable, advanced, or metastatic melanoma.

Keytruda is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following Yervoy therapy and, if BRAF V600 mutation positive, a BRAF inhibitor (e.g., Tafinlar, Zelboraf). This indication was approved as an accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

According to the National Comprehensive Cancer Network (NCCN) guidelines on melanoma (version 3.2015), patients with advanced or metastatic melanoma (distant metastatic disease [Stage IV]) can be managed by systemic therapy, clinical trial, and best supportive care. Symptomatic patients may receive palliative resection and/or radiation. First-line systemic therapy is based on factors such as BRAF mutation status, the tempo of the disease, and cancer-related symptoms. Clinical studies are underway to assess the optimal sequencing and/or combination of these agents. These guidelines recommend Keytruda as single-agent therapy for metastatic or unresectable disease as first-line therapy or as second-line therapy for disease progression or following maximum clinical benefit from BRAF targeted therapy for patients with performance status 0 to 2. In patients with metastatic or unresectable disease and BRAF V600 wild type, first-line systemic treatment options in patients who are anticipated to be clinically stable for > 12 weeks include Keytruda (category 2A), Opdivo* (nivolumab intravenous injection) [category 1], Yervoy (category 1), and high-dose Proleukin* (aldesleukin for intravenous infusion) [category 2A]. In patients who are anticipated to be clinically stable for ≤ 12 weeks, the first-line systemic treatment options include Keytruda (category 2A), Opdivo (category 1), cytotoxic agents (e.g., dacarbazine, temozolomide, paclitaxel), Gleevec* (imatinib mesylate tablets, category 2A) [for tumors with activating mutations of C-KIT], or biochemotherapy (category 2B) [e.g., dacarbazine or temozolomide with cisplatin/vinblastine with or without Proleukin and Intron A (interferon alfa-2b injection) or Sylatron* (peginterferon alfa-2b subcutaneous injection)]. Patients with disease progression on the previously described treatment options and who have performance status 0 to 2 may receive second-line or subsequent therapy with Keytruda, Opdivo, Yervoy (category 1), high-dose Proleukin, cytotoxic agents, Gleevec (for tumors with activating mutations of C-KIT), or biochemotherapy (category 2B). For patients with
CLINICAL COVERAGE CRITERIA

performance status 3 to 4 it is recommended to consider best supportive care. In patients with metastatic or unresectable disease and BRAF V600 mutant type (i.e., mutation positive), first-line systemic treatment options in patients who are anticipated to be clinically stable for > 12 weeks include Keytruda (category 2A), Opdivo (category 1), Yervoy (category 1), Tafinlar plus Mekinist® (trametinib tablets) [category 1], or high-dose Proleukin (category 2A). In patients who are anticipated to be clinically stable for ≤ 12 weeks, the first-line systemic treatment options include Tafinlar plus Mekinist (category 1) [preferred], Zelboraf (category 1), Tafinlar alone (category 1), Keytruda (category 2A), or Opdivo (category 1). Further recommendations are made in the guidelines for patients with disease progression or maximum clinical benefit from BRAF targeted therapy and who have a performance status of 0 to 2.

The efficacy of Keytruda was established in one pivotal, published, Phase I trial called KEYNOTE-001,1,3 which involved a cohort of patients with progressive, unresectable melanoma that was previously treated with at least two doses of Yervoy 3 mg/kg or higher given every 3 weeks and also previously treated with BRAF and/or mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors if the patient had BRAF-mutant melanoma. In another cohort of patients in this study, additional safety information and tumor responses were provided in patients with advanced melanoma who had disease progression while receiving Yervoy or who had not received Yervoy.4

Dosing in Advanced, Unresectable or Metastatic Melanoma in Adults. Dosing must meet the following: 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks.-

The recommended dose is 2 mg/kg given as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.1 There are no recommended dose reductions in the prescribing information. Management of adverse events may require that Keytruda be withheld or permanently discontinued as determined by the prescribing physician.

Initial Approval/Extended Approval.
A) Initial Approval: Approve for 6 months.
B) Extended Approval: Approve at 6-month intervals if the patient has a response as determined by the prescribing physician.

Duration of Therapy in Advanced, Unresectable or Metastatic Melanoma in Adults. Indefinite if the patient is responding to therapy.

In KEYNOTE-001, 411 patients with unresectable or metastatic melanoma received Keytruda at either 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks.1 The median duration of exposure was 6.2 months (range, 1 day to 24.6 months) with a median of 10 doses (range, 1 to 51 doses).

Labs/Diagnostics. None required.
2. **Patient has been Started on Keytruda.** Approve if the patient meets the conditions for coverage required for Dosing, Extended Approval, Duration of Therapy, and Labs/Diagnostics for an approved use in this Keytruda Utilization Review policy.

3. **Other Cancer-Related Indications.** Forward to the Medical Director for review on a case-by-case basis.

**Waste Management for All Indications.**
Dosing for Keytruda is based on body weight (mg/kg). The dose should be calculated and the number of vials needed assessed.

**Conditions Not Recommended for Approval**
Keytruda has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

**SPECIAL CONSIDERATIONS**
None

**LIMITATIONS/EXCLUSIONS**
Please refer to each product line’s certificate of coverage for benefit limitations and exclusions for these services.

**REFERENCES**

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CONTRACTCITATION

- APPLE HEALTH MEDICAID
- MEDICARE ADVANTAGE

OTHER REQUIREMENTS

NCQA ELEMENTS

REVISION HISTORY

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