Yervoy (ipilimumab)

**Policy**
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Yervoy when it is determined to be medically necessary because the following criteria have been met.

**When Policy Topic is covered**

**FDA Approved Indications:**

1. Yervoy may be considered **medically necessary** in patients 18 years of age or older for unresectable melanoma or metastatic melanoma; agreement to permanently discontinue Yervoy if full treatment course is not completed within 16 weeks of administration of first dose;

2. Yervoy also may be considered **medically necessary** in patients 18 years of age or older for cutaneous melanoma as adjuvant therapy in patients with pathologic involvement of regional lymph nodes of more than 1 mm and the patient has undergone complete resection, including total lymphadenectomy; agreement to permanently discontinue Yervoy and initiate corticosteroid therapy for severe immune-mediated reactions; clinical chemistries, including liver and thyroid function tests, are evaluated at baseline and before each dose.

3. Yervoy is considered **medically necessary** in combination with nivolumab for previously untreated patients with intermediate and poor risk advanced renal cell carcinoma (RCC).

**Off-Label Uses with supporting evidence:**

1. Unresectable or metastatic melanoma, first-line combination therapy with nivolumab.

2. Retreatment of melanoma in patients who experience disease control but who relapse or progress greater than 3 months after treatment discontinuation.

3. Central nervous system (CNS) metastases if active against primary tumor (melanoma)

4. Small cell lung cancer (SCLC) in combination with nivolumab

5. Malignant pleural mesothelioma in combination with nivolumab

**DOSING:**
Adult FDA-approved uses:
See FDA labeling

Doses of 10mg/kg may qualify for manufacturer free drug program, shipped directly to provider. This dose will be considered for coverage only with evidence that patient does NOT qualify for manufacturer’s free drug program.
Pediatric FDA-approved uses:
Safety and effectiveness have not been established

**Drug must be sourced from an approved specialty infusion provider.**

**When Policy Topic is not covered**
Yervoy may be considered *investigational* in patients less than 18 years of age and all other indications.

Without evidence that patient does NOT qualify for manufacturer’s free drug program, the 10mg/kg will be considered *not medically necessary*.

**Considerations**
Yervoy requires prior authorization through the Clinical Pharmacy Department.

This Blue Cross and Blue Shield of Kansas City policy Statement was developed using available resources such as, but not limited to: Food and Drug Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers.

**Description of Procedure or Service**

**Background**
Yervoy (ipilimumab) is a monoclonal antibody used to treat patients with unresectable or metastatic (late-stage) melanoma. Yervoy blocks a molecule known as CTLA-4 (cytotoxic T-lymphocyte antigen). CTLA-4 may play a role in slowing down or turning off the body’s immune system, affecting its ability to fight off cancerous cells. Yervoy may work by allowing the body’s immune system to recognize, target, and attack cells in melanoma tumors. The drug is administered intravenously (1).

**Regulatory Status**
FDA-approved indication: Yervoy is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)- blocking antibody indicated for: (1)
1. Treatment of unresectable or metastatic melanoma
2. Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy

Off-Label Uses: (2)
1. Melanoma, unresectable or metastatic, first line combination therapy with nivolumab
2. Retreatment of melanoma in patients who experience disease control but who relapse or progress greater than 3 months after treatment discontinuation
3. Central nervous system (CNS) metastases if active against primary tumor (melanoma)
4. Small cell lung cancer (SCLC) in combination with nivolumab

Yervoy has a boxed warning of severe and fatal immune-mediated adverse reactions due to Tcell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab. Permanently discontinue ipilimumab and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions. Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests and thyroid function tests at baseline and before each dose (1).
Due to the unusual and severe side effects associated with Yervoy, the drug is approved with a Risk Evaluation and Mitigation Strategy (REMS) program to help doctors avoid and manage adverse reactions including educating patients regarding the signs and symptoms of immunemediated adverse reactions and what to do if they occur as is outlined on the Patient Wallet Card (1).

Yervoy should be permanently discontinued for failure to complete a full treatment course within 16 weeks from administration of first dose (1).

Safety and effectiveness of Yervoy have not been established in pediatric patients (1).

**Rationale**

Yervoy is a monoclonal antibody used to treat patients with unresectable or metastatic (late-stage) melanoma, and cutaneous melanoma (stage III). Yervoy has a boxed warning of severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. The most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy.

Prior authorization is required to ensure the safe, clinically appropriate and cost-effective use of Yervoy while maintaining optimal therapeutic outcomes.

**References**


**Billing Coding/Physician Documentation Information**

| J9228 | Injection, ipilimumab, 1 mg |
C43+ Malignant melanoma of skin
C51+ Malignant neoplasm of vulva
C52 Malignant neoplasm of vagina
C60+ Malignant neoplasm of penis
C63+ Malignant neoplasm of other and unspecified male genital organs

Additional Policy Key Words
5.02.532

Policy Implementation/Update Information

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/2017</td>
<td>New policy titled Yervoy (ipilimumab)</td>
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<tr>
<td>10/2017</td>
<td>Added off-label indications with supporting evidence</td>
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<tr>
<td>03/2018</td>
<td>Reviewed – no changes made</td>
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<tr>
<td>06/2018</td>
<td>Added new indication for RCC and removed drug assistance program requirement.</td>
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<tr>
<td>03/2019</td>
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State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.