VENTURA COUNTY HEALTH CARE PLAN

Utilization Review Policy

POLICY: Oncology – Kyprolis (carfilzomib injection for intravenous use – Amgen/Onyx Pharmaceuticals)

APPROVAL DATE: 02/20/2019

OVERVIEW

Kyprolis is an irreversible proteasome inhibitor that inhibits proteasome activity in blood and tissue and delays tumor growth.[1] It is indicated for treatment of multiple multiple myeloma in the following situations:

1. in combination with dexamethasome ± Revlimid® (lenalidomide capsules) for relapsed or refractory multiple myeloma, who have received one to three lines of previous therapy.
2. As a single agent for the treatment of relapsed or refractory multiple myeloma who have received one or more lines of therapy.

Guidelines

The NCCN Multiple Myeloma clinical practice guidelines (version 2.2019 – November 16, 2018) recommend Kyprolis in treatment regimens for patients who are transplant and non-transplant candidates.[3] Kyprolis/Revlimid/dexamethasone is recommended as an Other Recommended Regimen for primary treatment in transplant candidates. In non-transplant candidates, Kyprolis/dexamethasone plus Revlimid or cyclophosphamide is a recommended Other Recommended Regimen for primary treatment. For previously treated multiple myeloma, Kyprolis/dexamethasone/Revlimid is among the Preferred regimens, whereas Kyprolis/dexamethasone ± cyclophosphamide, Kyprolis/Farydak (panobinostat capsules), and Kyprolis/dexamethasone/Pomalyst (pomalidomide capsules) are listed as Other Recommended Regimens.

In NCCN guidelines for Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lympohoma (version 2.2019), Kyprolis/Rituxan (rituximab infusion)/dexamethasone is listed among other recommended regimens for primary treatment of Waldenstrom's Magroglobulinemia/lymphoplasmacytic lymphoma.[4]

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Kyprolis. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below.

Because of the of the specialized skills required for evaluation and diagnosis of patients treated with Kyprolis, as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Kyprolis to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

1. **Multiple Myeloma**. Approve for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** The patient meets ONE of the following (i or ii):
     - **i.** Kyprolis will be used in combination with dexamethazone AND at least one other agent (e.g., Revlimid® [lenalidomide capsules], cyclophosphamide); OR
     - **ii.** The patient meets BOTH of the following (a and b):
       - **a)** The patient has tried at least one other regimen for multiple myeloma (e.g., regimens containing one or more of the following agents: Velcade [bortezomib injection], Revlimid [lenalidomide capsules], dexamethasone, cyclophosphamide, Darzalex [daratumumab injection], Pomalyst [pomalidomide capsules], Farydak [panobinostat capsules]); AND
       - **b)** Kyprolis is being used in combination with at least one other agent (e.g., dexamethasone, Revlimid [lenalidomide capsules], cyclophosphamide, Farydak [panobinostat capsules], Pomalyst [pomalidomide capsules]); AND
   - **B)** The agent is prescribed by or in consultation with an oncologist or a hematologist.

   Dosing. Approve if the requested dosing meets the following (A and B):
   - **A)** Each single dose must not exceed 70 mg/m^2; AND
   - **B)** The patient receives a maximum of six infusions per 28-day treatment cycle.

   Dosing regimen is individualized. Refer to the Appendix for more specific dosing regimens recommended in the prescribing information. Note: Dose modifications of Kyprolis are recommended for the management of hematological toxicity (e.g., neutropenia, thrombocytopenia), renal toxicity, other non-hematological toxicity, and hepatic impairment. This may include reducing the dose in levels (to a minimum of 15 mg/m^2) or withholding the drug until the toxicity is resolved. See the prescribing information for more detail.

   In some cases, treatment is continued until disease progression or unacceptable toxicity. Therapy is individualized with careful consideration of the risks and benefits of continued treatment.

Other Uses with Supportive Evidence

2. **Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** Kyprolis will be used in combination with rituximab (e.g., Rituxan intravenous) and dexamethasone; AND
   - **B)** The agent is prescribed by or in consultation with an oncologist or a hematologist.

   Dosing. Approve if the requested dosing meets the following (A and B):
   - **A)** Each single dose must not exceed 70 mg/m^2; AND
   - **B)** The patient receives a maximum of six infusions per 28-day treatment cycle.

   Limited dosing is available. Single doses up to 70 mg/m^2 administered a maximum of twice weekly are recommended in the product labeling for approved uses.[1] Refer to the Appendix for more specific dosing as documented in the prescribing information for approved indications. In patients who respond to therapy, patients may be followed with observation. Treatment decisions, including duration of therapy, are individualized with careful consideration of the risks and benefit of the selected regimen.

In a small Phase II study, Kyprolis was administered with Rituxan and dexamethasone for patients with as Waldenstrom's macroglobulinemia.[5] During Cycle 1, the dose of Kyprolis was 20 mg/m^2. During Cycles 2 through 6, the dose of Kyprolis was 36 mg/m^2 on Days 1, 2, 8, and 9 of each 21-day cycle. This was followed by maintenance dosing (8 weeks later) with Kyprolis at a dose of 36 mg/m^2 on Days 1 and 2 every 8 weeks for 8 cycles.

Note: Dose modifications of Kyprolis are recommended for the management of hematological toxicity (e.g., neutropenia, thrombocytopenia), renal toxicity, other non-hematological toxicity, and hepatic impairment. This may include reducing the dose in levels (to a minimum of 15 mg/m^2) or withholding the drug until the toxicity is resolved. See the prescribing information for more detail.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Kyprolis 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.)

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

REFERENCES

1. Kyprolis® injection for intravenous use [prescribing information]. Onyx Pharmaceuticals/Amgen: Thousand Oaks, CA.; September 2018.
2. The NCCN Drugs and Biologics Compendium. © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 8, 2019. Search term: carfilzomib.
3. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (Version 2.2019 – November 16, 2018). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 8, 2019.
4. The NCCN Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (Version 2.2019 – September 14, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 8, 2019.
5. Treon SP, Tripsas CK, Meid K, et al. Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenström's macroglobulinemia. *Blood*. 2014;124(4):503-510.

HISTORY

Type of Revision	Summary of Changes*	Approval Date
New policy	--	11/14/2018
Early annual revision	**Multiple Myeloma:** When previous therapy is required, reword criterion to require at least one regimen for multiple myeloma (previous worded as at least one therapy).	02/20/2019

APPENDIX

Table 1. Approved Kyprolis Dosing When Administered with Dexamethasone.*

Kyprolis Regimen	Cycle 1								
	Day 1	**Day 2**	**Days 3-7**	**Day 8**	**Day 9**	**Days 10-14**	**Day 15**	**Day 16**	**Days 17-28**
Kyprolis once weekly regimen	20 mg/kg	--	--	70 mg/kg	--	--	70 mg/kg	--	--
Kyprolis twice weekly regimen	20 mg/kg	20 mg/kg	--	56 mg/kg	56 mg/kg	--	56 mg/kg	56 mg/kg	--
Kyprolis Regimen	**Cycles 2 through 9**								
Kyprolis once weekly regimen	70 mg/kg	--	--	70 mg/kg	--	--	70 mg/kg	--	--
Kyprolis twice weekly regimen	56 mg/kg	56 mg/kg	--	56 mg/kg	56 mg/kg	--	56 mg/kg	56 mg/kg	--
Kyprolis Regimen	**Cycles 10 and later**								
Kyprolis once weekly regimen	70 mg/kg	--	--	70 mg/kg	--	--	70 mg/kg	--	--
Kyprolis twice weekly regimen	56 mg/kg	56 mg/kg	--	56 mg/kg	56 mg/kg	--	56 mg/kg	56 mg/kg	--

* Refer to the Kyprolis prescribing information for recommended dose modifications based on toxicity and for dosing schedule for concomitant dexamethasone.

Table 2. Approved Kyprolis Dosing When Administered with Revlimid and Dexamethasone.*

Kyprolis Regimen	Cycle 1								
	Day 1	**Day 2**	**Days 3-7**	**Day 8**	**Day 9**	**Days 10-14**	**Day 15**	**Day 16**	**Days 17-28**
Kyprolis twice weekly regimen	20 mg/kg	20 mg/kg	--	27 mg/kg	27 mg/kg	--	27 mg/kg	27 mg/kg	--
Kyprolis Regimen	**Cycles 2 through 12**								
Kyprolis once weekly regimen	27 mg/kg	27 mg/kg	--	27 mg/kg	27 mg/kg	--	27 mg/kg	27 mg/kg	--
Kyprolis Regimen	**Cycles 13 and later^**								
Kyprolis once weekly regimen	27 mg/kg	27 mg/kg	--	--	--	--	27 mg/kg	27 mg/kg	--

* Refer to the Kyprolis prescribing information for recommended dose modifications based on toxicity and for dosing schedule for Revlimid and dexamethasone.
^ Kyprolis is administered through Cycle 18.

Table 3. Approved Kyprolis Dosing When Administered as Monotherapy.*

Kyprolis Regimen	Cycle 1								
	Day 1	**Day 2**	**Days 3-7**	**Day 8**	**Day 9**	**Days 10-14**	**Day 15**	**Day 16**	**Days 17-28**
Kyprolis 20/27 mg/kg regimen	20 mg/kg	20 mg/kg	--	27 mg/kg	27 mg/kg	--	27 mg/kg	27 mg/kg	--
Kyprolis 20/56 mg/kg regimen	20 mg/kg	20 mg/kg	--	56 mg/kg	56 mg/kg	--	56 mg/kg	56 mg/kg	--
Kyprolis Regimen	**Cycles 2 through 12**								
Kyprolis 20/27 mg/kg regimen	27 mg/kg	27 mg/kg	--	27 mg/kg	27 mg/kg	--	27 mg/kg	27 mg/kg	--
Kyprolis 20/56 mg/kg regimen	56 mg/kg	56 mg/kg	--	56 mg/kg	56 mg/kg	--	56 mg/kg	56 mg/kg	--
Kyprolis Regimen	**Cycles 13 and later**								
Kyprolis 20/27 mg/kg regimen	27 mg/kg	27 mg/kg	--	--	--	--	27 mg/kg	27 mg/kg	--
Kyprolis 20/56 mg/kg regimen	56 mg/kg	56 mg/kg	--	56 mg/kg	56 mg/kg	--	56 mg/kg	56 mg/kg	--

* Refer to the Kyprolis prescribing information for recommended dose modifications based on toxicity.