panobinostat (Farydak®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO196

Description

Panobinostat (Farydak) is an orally administered histone deacetylase inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: Six months (can only be renewed once)

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
panobinostat (Farydak)	10 mg capsules	Multiple Myeloma with ≥2 prior regimens, including bortezomib and an immunomodulatory agent	6 capsules/21 days
	15 mg capsules		
	20 mg capsules		

Initial Evaluation

I. Panobinostat (Farydak) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a hematologist or oncologist; **AND**
   C. Not used in combination with any other oncology therapy unless outlined below; **AND**
   D. A diagnosis of **multiple myeloma** when the following are met:
      1. Provider attests member has received at least two prior regimens including both of the following:
         i. Bortezomib (Velcade); **AND**
         ii. Immunomodulatory agent (e.g., thalidomide, lenalidomide, pomalidomide); **AND**
      2. Provider attests panobinostat (Farydak) will be used in combination with one of the following:
         i. Bortezomib (Velcade) AND dexamethasone *only*; **OR**
         ii. Lenalidomide (Revlimid) AND dexamethasone *only*; **OR**
         iii. Carfilzomib (Kyprolis) *only*

II. Panobinostat (Farydak) is considered investigational when used for all other conditions, including but not limited to:
   A. Multiple myeloma when given as part of a quadruplet ("quad") regimen

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Medication is prescribed by, or in consultation with, an oncologist; **AND**
III. Member is responsive to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
IV. Member will not receive more than a total treatment duration of 48 weeks; **AND**
V. Provider attests panobinostat (Farydak) will be used in combination with one of the following:
   A. Bortezomib (Velcade) AND dexamethasone *only*; **OR**
   B. Lenalidomide (Revlimid) AND dexamethasone *only*; **OR**
   C. Carfilzomib (Kyprolis) *only*

Supporting Evidence

I. Panobinostat (Farydak) is FDA-approved for use in combination with bortezomib and dexamethasone and is indicated in the treatment of patients with multiple myeloma who have received at least two prior regimens, including bortezomib and an immunomodulatory agent. This indication is approved under accelerated approval based on progression free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
II. The recommended starting dose of panobinostat (Farydak) is 20 mg, taken orally once every other day for three doses per week (on Days 1, 3, 5, 8, 10, and 12) of Weeks 1 and 2 of each 21-day cycle for eight cycles. Treatment continuation may be considered for an additional eight cycles (total 16 cycles) for patients with clinical benefit, unless they have unresolved severe or medically significant toxicity. The total duration of treatment may be up to 16 cycles (48 weeks).
III. Panobinostat (Farydak) was studied in 768 subjects from one Phase 3, double-blind, placebo-controlled, multicentered, multi-country trial. The trial included subjects with one to three previous treatments. Subjects were randomized 1:1 to receive panobinostat (Farydak) + bortezomib and dexamethasone (PAN-BTZ-Dex) or placebo + bortezomib and dexamethasone (PBO-BTZ-Dex) stratified by prior use of bortezomib and the number of prior lines of anti-myeloma therapy. The primary endpoint was progression free survival (PFS), and a key secondary endpoint was overall survival (OS).

- Median PFS was 11.99 months (95% CI 10.33-12.94) PAN-BTZ-Dex compared to 8.08 months (95% CI 7.56-9.23) PBO-BTZ-Dex, with HR 0.63 (95% CI 0.52-0.76) p<0.0001.

	Median Progression-Free Survival (95% CI, mo [n])		Hazard Ratio (95% CI)
	PAN-BTZ-Dex	Placebo-BTZ-Dex	
Prior use of immunomodulatory drugs (n=485)	13.14 (11.56-15.47)	10.41 (7.95-11.53)	0.54 (0.43-0.68)
Prior use of immunomodulatory drugs and bortezomib (n=193)	11.99 (9.69-13.90)	8.31 (6.14-12.32)	0.52 (0.36-0.76)
Previous use of immunomodulatory drugs, bortezomib, and two or more lines (n=147)	11.99 (9.69-13.37)	6.97 (4.86-13.40)	0.47 (0.31-0.72)

- Matured median OS was 40.3 months (95% CI 35-44.8) PAN-BTZ-Dex compared to 35.8 months (95% CI 29-40.6) PBO-BTZ-Dex, with HR 0.94 (95% CI 0.78–1.14) p=0.54.

	Median Overall Survival (95% CI, mo [n])		Hazard Ratio (95% CI)
	PAN-BTZ-Dex	Placebo-BTZ-Dex	
Prior use of immunomodulatory drugs (n=485)	36.2 (31.18–41.36)	29.4 (24.57–37.78)	0.94 (0.74–1.19)
Prior use of immunomodulatory drugs and bortezomib (n=193)	27.2 (24.21–34.63)	24.7 (17.48–35.38)	1.03 (0.72–1.47)
Previous use of immunomodulatory drugs, bortezomib, and two or more lines (n=147)	25.5 (19.58–34.33)	25.5 (19.58–34.33)	1.01 (0.68–1.50)

IV. Although the clinical trial evaluated subjects with one to three previous treatments, as stated in the package insert, the approval of panobinostat (Farydak) was based upon the efficacy and safety in a prespecified subgroup analysis of 193 patients who had received prior treatment with both bortezomib and an immunomodulatory agent and a median of two prior therapies as the benefit to risk profile appeared to be greater in this more heavily pretreated population than in the overall trial population.

V. Panobinostat (Farydak) is associated with significant toxicity. Clinical trial discontinuation rate was 36% in the panobinostat (Farydak) group, due to adverse events, as compared to 20% in the placebo group. Moreover, discontinuation rate due to Grades 3 or 4 adverse events was 25% in the panobinostat (Farydak) group compared to 13% in the placebo group. However, split fill management is not applicable because only a total of six panobinostat (Farydak) capsules are given per 21-day cycle.

VI. Panobinostat (Farydak) is a REMS agent, carrying a black box warning for fatal and serious toxicities of severe diarrhea and cardiac toxicities.
- Common adverse events (≥20%) are diarrhea, fatigue, nausea, peripheral edema, decreased appetite, pyrexia, and vomiting.
- Common non-hematologic abnormalities (≥40%) are hypophosphatemia, hypokalemia, hyponatremia, and increased creatinine.
- Common hematologic abnormalities (≥60%) are thrombocytopenia, lymphopenia, leukopenia, neutropenia, and anemia.

VII. Per NCCN V2.2021 guidelines, panobinostat (Farydak) + bortezomib and dexamethasone is a Category 1 "other recommended regimen" for previously treated multiple myeloma. Other combinations that do not include panobinostat (Farydak) are considered "preferred". NCCN guidelines recommend that panobinostat (Farydak) + carfilzomib (Category 2A) OR panobinostat + lenalidomide and dexamethasone (Category 2A) may be useful in certain circumstances and state that such treatment is only indicated for patients who have received at least two prior therapies, including bortezomib and an immunomodulatory agent; guidelines do not define circumstances.
- Panobinostat (Farydak) + lenalidomide and dexamethasone was studied in a multicenter phase I/II study. Primary endpoint of phase II was ORR, which was 82%, and the clinical benefit rate was 91%.
- Panobinostat (Farydak) + carfilzomib was studied in a single-center, phase II study in 27 patients. Primary endpoint was ORR, which was 41%. PFS was 7.1 months.

Investigational or Not Medically Necessary Uses

I. Panobinostat (Farydak) has not been sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Quadruple ("quad") regimen
      i. Although triplet regimens remain the standard of care for multiple myeloma, there is growing interest in quad regimens which may include the addition of monoclonal antibodies (e.g., daratumumab [Darzalex], elotuzumab [Empliciti]) to standard triplet backbone regimens. The current evidence available to support this use is limited to case series or small trials. Larger studies evaluating the safety and efficacy of these regimens are underway.

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Appendix

I. Table 1: Recommended Dosing Schedule of panobinostat (Farydak) in Combination with Bortezomib and Dexamethasone During Cycles 1 to 8

21-Day Cycle															
Cycles 1 to 8 (3-Week cycles)	Week 1 Days						Week 2 Days						Week 3		
FARYDAK	1		3		5		8		10		12		Rest period		
Bortezomib	1			4			8			11			Rest period		
Dexamethasone	1	2		4	5		8	9		11	12		Rest period		

II. Table 2: Recommended Dosing Schedule of panobinostat (Farydak) in Combination with Bortezomib and Dexamethasone During Cycles 9 to 16

21-Day Cycle															
Cycles 9 to 16 (3-Week cycles)	Week 1 Days						Week 2 Days						Week 3		
FARYDAK	1		3		5		8		10		12		Rest period		
Bortezomib	1						8						Rest period		
Dexamethasone	1	2					8	9					Rest period		

III. Table 3: Classification of Medications used for Multiple Myeloma

Proteasome Inhibitors	Immunomodulatory Agents	Monoclonal Antibodies	Histone Deacetylase Inhibitors	B-cell Maturation Antigen-Directed Antibody	Chemotherapy
• bortezomib • carfilzomib • ixazomib	• thalidomide • lenalidomide • pomalidomide	• elotuzumab • daratumumab • isatuximab-irfc	• panobinostat	• belantamab mafodotin-blmf	• cyclophosphamide • doxorubicin • cisplatin • etoposide • melphalan • bendamustine

References

1. Farydak [Prescribing Information]. Las Vegas, NV: Secura Bio, Inc. September 2019.
2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Multiple Myeloma Version 2.2021. 2020 September 9; National Comprehensive Cancer Network. Available from: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria transitioned to policy format. Removed requirements around counseling on side effects and attesting to lack of recent myocardial infarction or unstable angina. Addition of supporting evidence and	10/2020

additional combination agent options [addition of lenalidomide (Revlimid) and dexamethasone; or carfilzomib (Kyprolis)].	
Criteria created	03/2015