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Reviewed: 06/12/19

Revised: 07/15/19

Subject: Panobinostat (Farydak®) Capsule

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Panobinostat (Farydak) is a first-in-class, oral histone deacetylase (HDAC) inhibitor. Inhibition of HDAC activity results in increased acetylation of histone proteins ultimately leading to cell cycle arrest and/or apoptosis of certain cancer cells. Panobinostat was approved by the FDA in February 2015 for the treatment of patients with multiple myeloma (MM) who have received at least two prior regimens, including bortezomib (Velcade) and an immunomodulatory agent. This was an accelerated approval based on progression-free survival (PFS) improvement, and continued approval may be dependent upon verification of clinical benefit in a confirmatory trial. The FDA previously granted panobinostat orphan designation for the treatment of MM in 2012.

The safety and efficacy of panobinostat were evaluated in a multinational, randomized, double-blind, phase III trial (PANORAMA 1) in which treatment with panobinostat, bortezomib, and dexamethasone (n=387) was compared to placebo, bortezomib, and dexamethasone (n=381) in patients with relapsed or relapsed and refractory multiple myeloma who had received one to three prior therapies. Treatment was administered for a maximum of 16 cycles (48 weeks).The median number of prior therapies was 1; 48% of patients received 2 or 3 prior lines of therapy. Approximately 57% of patients had previously received a stem-cell transplantation. At a median follow-up time of 29 months, the median PFS was significantly improved in the panobinostat arm (12 months) vs. the placebo arm (8.1 months) [hazard ratio (HR) = 0.63; 95% CI, 0.52 to 0.76]. Overall survival (OS) was not significantly improved at the interim analysis, but the data were premature for the OS analysis. Of note, the approval of panobinostat was based upon 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 ratio appeared to be greater in this more heavily pretreated population (PFS of 12.5 months vs. 4.7 months in placebo group) as compared to the overall trial population. In December 2015, the overall survival results were released. For the overall study population, patients in the panobinostat group demonstrated a non-

statistically significant increase in median OS of 4.5 months vs, the placebo group (p=0.54). However, more patients in the placebo group received post-study therapy (48.8% vs. 37.7%) that may have confounded the OS results.

The National Comprehensive Cancer Network (NCCN) Guidelines for MM (Version 2.2019) list numerous combination treatments under "Preferred Regimens" as category 1 recommendations for patients with disease relapse or disease progression (i.e., previously treated MM). Under "Other Recommended Regimens" for previously treated MM, the guidelines list the triplet regimen of panobinostat + bortezomib + dexamethasone as a category 1 recommendation, the triplet regiment of panobinostat + lenalidomide (Revlimid) + dexamethasone as a category 2A recommendation, and the doublet regimen of panobinostat + carfilzomib (Kyprolis) as a category 2A recommendation. All of the regimens include a footnote of "indicated for the treatment of patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent".

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of panobinostat (Farydak) **meets the definition of medical necessity** when **EITHER** of the following are criteria met ("1" or "2"), **AND** the member's baseline Fridericia's corrected QT interval (QTcF) is less than 450 msec:

1. The member has a diagnosis of relapsed or refractory multiple myeloma (MM), and **ALL** of the following are met ("a" to "e"):
    a. The member has been previously treated for MM with at least **TWO** separate lines of therapy
    b. The member has been previously treated for MM with **BOTH** of the following ("i" and ii"):
        i. Bortezomib **OR** ixazomib (Ninlaro)
        ii. At least **ONE** of the following immunomodulatory agents:
            - Lenalidomide (Revlimid)
            - Pomalidomide (Pomalyst)
            - Thalidomide (Thalomid)
    c. The member is to receive panobinostat in combination with **ANY** of the following:
        i. Both bortezomib and dexamethasone
        ii. Both lenalidomide and dexamethasone
        iii. Carfilzomib (Kyprolis)
    d. The member's baseline (i.e., within 90 days prior to initiating treatment with panobinostat) serum monoclonal protein (M-protein) level, as detected by serum protein electrophoresis (SPEP), is provided*

        *If the M-protein is undetectable by SPEP, baseline serum free light chain (SFLC) levels (kappa and lambda, as detected by serum free light chain assay (SFLCA), must also be provided

e. The dosage of panobinostat does not exceed the following based on the drug regimen used:
    i. Panobinostat + bortezomib + dexamethasone - one capsule (all strengths) for six doses during each 21-day cycle (e.g., days 1, 3, 5, 8, 10, and 12)
    ii. Panobinostat + lenalidomide + dexamethasone – one capsule (all strengths) for six doses during each 28-day cycle (e.g., days 1, 3, 5, 15, 17, and 19)
    iii. Panobinostat + carfilzomib - one capsule (all strengths) for six doses during each 28-day cycle (e.g., days 1, 3, 5, 15, 17, and 19)

2. Other FDA-approved or NCCN supported diagnosis (not previously listed above), and BOTH of the following ("a" and "b"):

a. **EITHER** of the following is met ("i or "ii"):

    i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)

    ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

b. The dosage of panobinostat does not exceed the maximum recommended in the FDA-approved prescribing information or the maximum recommended by the applicable NCCN guidelines for the indication

Duration of approval: 6 months

Continuation of panobinostat (Farydak**) meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "6"):

1. An authorization or reauthorization for panobinostat has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of MM, or other FDA-approved or NCCN-supported diagnosis; **OR** the member previously met **ALL** indication-specific initiation criteria
2. The member is using ANY of the following drug regimens based on the indication:
    a. Multiple myeloma
        i. Both bortezomib and dexamethasone
        ii. Both lenalidomide and dexamethasone
        iii. Carfilzomib
    b. Other FDA-approved or NCCN-supported diagnosis (not listed above) - panobinostat is used in a treatment regimen in accordance with the FDA-approved package labeling or NCCN guideline recommendation
3. The dosage of panobinostat does not exceed the following based on the indication and drug regimen used:
    a. Multiple myeloma
        i. Panobinostat + bortezomib + dexamethasone - one capsule (all strengths) for six doses during each 21-day cycle (e.g., days 1, 3, 5, 8, 10, and 12)

ii. Panobinostat + lenalidomide + dexamethasone – one capsule (all strengths) for six doses during each 28-day cycle (e.g., days 1, 3, 5, 15, 17, and 19)

iii. Panobinostat + carfilzomib - one capsule (all strengths) for six doses during each 28-day cycle (e.g., days 1, 3, 5, 15, 17, and 19)

b. Other FDA-approved or NCCN-supported diagnosis (not listed above) - the maximum recommended in the FDA-approved prescribing information or the maximum recommended by the applicable NCCN guidelines for the indication

4. The member is not experiencing unresolved severe [i.e., Common Terminology Criteria for Adverse Events (CTCAE) Grade 3] or medically significant toxicity from the previous cycle of panobinostat treatment
5. The member's most recent Fridericia's corrected QT interval (QTcF) is less than 480 msec
6. Member meets **EITHER** of the following based on the indication for use ("a" or "b"):

   a. Multiple myeloma

      i. If less than 18 months of treatment - a serum M-protein level decrease of 25% or more* compared to baseline, or M-protein is undetectable; **AND** no increase in the size or number of lytic bone lesions after at least two cycles of treatment with ixazomib[†,#]

      ii. 18 months or more of treatment - provider attestation that the member has not had disease progression during panobinostat treatment

   b. Other FDA-approved or NCCN-supported diagnosis (not listed above) - provider attestation that the member has not had disease progression during pomalidomide treatment

   **If the M-protein was undetectable by SPEP at baseline and a baseline SFLC level is available, a decrease of 25% or more in the difference between the light chain produced by the myeloma cells (lambda or kappa) and the other light chain must be achieved*

   [†]If the M-protein was undetectable by SPEP at baseline and a baseline SFLC level is available, a follow-up SFLC level must be submitted

   [#]An exception is permitted if a baseline M-protein level AND SFLC level are unavailable. In these cases the physician may provide an attestation of a beneficial clinical response which must include no increase in the size or number of lytic bone lesions.

Duration of approval: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Panobinostat, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma who have received at least two prior regimens, including bortezomib and an immunomodulatory agent.
- The recommended starting dose of panobinostat is 20 mg orally once every other day for 3 doses per week in Weeks 1 and 2 of each 21-day cycle (on Days 1, 3, 5, 8, 10, and 12) for up to 8 cycles. Swallow capsules whole with a full glass of water; do not open, crush, or chew capsules. Consider continuing treatment for an additional 8 cycles for patients with clinical benefit who do not experience

unresolved severe or medically significant toxicity. The total duration of treatment may be up to 16 cycles (48 weeks). Panobinostat is administered in combination with bortezomib and dexamethasone. The recommended dose of bortezomib is 1.3 mg/m^2 given as an injection. The recommended dose of dexamethasone is 20 mg orally per scheduled day, on a full stomach. View the prescribing information for the complete dosing recommendations.

Dose Adjustments

- **Toxicity** - Management of adverse drug reactions may require treatment interruption and/or dose reductions. If dose reduction is required, the dose of panobinostat should be reduced in increments of 5 mg (i.e., from 20 mg to 15 mg, or from 15 mg to 10 mg). If the dosing is to be reduced below 10 mg given 3 times per week, discontinue treatment. View the prescribing information for the complete dosing recommendations.
    - Thrombocytopenia [platelets <50 x 10^9/L (CTCAE Grade 3) with bleeding, or platelets <25 x 10^9/L (CTCAE Grade 4)]
        - Interrupt panobinostat treatment
        - Monitor platelet counts at least weekly until ≥50 x 10^9/L, then restart at reduced dose
    - Neutropenia [absolute neutrophil count (ANC) 0.5 to 0.75 x 10^9/L (CTCAE Grade 3) on two or more occurrences)]
        - Interrupt panobinostat treatment
        - Monitor until ANC ≥1 x 10^9/L, then restart at same dose
    - Neutropenia [ANC <1 x 10^9/L (CTCAE Grade 3) with febrile neutropenia, or ANC <0.5 x 10^9/L (CTCAE Grade 4)]
        - Interrupt panobinostat treatment
        - Monitor until ANC ≥1 x 10^9/L, then restart at reduced dose
    - Amenia [hemoglobin <8 g/dL (CTCAE Grade 3)]
        - Interrupt panobinostat treatment
        - Monitor until Hb ≥10 g/dL, then restart at reduced dose
    - Moderate diarrhea [4 to 6 stools/day (CTCAE Grade 2)]
        - Interrupt panobinostat treatment until resolved
        - Restart at same dose.
    - Severe diarrhea [≥7 stools/day, IV fluids, or hospitalization required (CTCAE Grade 3)]
        - Interrupt panobinostat treatment until resolved
        - Restart at reduced dose
    - Life-threatening Diarrhea (CTCAE Grade 3)
        - Permanently discontinue panobinostat treatment
    - Nausea or Vomiting [severe or life-threatening (CTCAE Grade 3/4)]
        - Interrupt panobinostat treatment until resolved
        - Restart at reduced dose
- **Hepatic Impairment**
    - Mild (Child-Pugh Class A)
        - Reduce the starting dose to 15 mg

- Moderate (Child-Pugh Class B)
  - Reduce the starting dose to 10 mg
- Severe (Child-Pugh Class C)
  - Avoid use

- **Use with Strong CYP3A Inhibitors** (e.g., boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir)
  - Reduce the starting dose to 10 mg

Drug Availability

- Panobinostat is available in 6-count blister packs containing 10-, 15-, or 20-mg capsules.

PRECAUTIONS:

Boxed Warning

- **FATAL AND SERIOUS TOXICITIES: SEVERE DIARRHEA AND CARDIAC TOXICITIES**
  - Severe diarrhea occurred in 25% of panobinostat treated patients. Monitor for symptoms, institute antidiarrheal treatment, interrupt panobinostat and then reduce dose or discontinue panobinostat.
  - Severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes have occurred in patients receiving panobinostat. Arrhythmias may be exacerbated by electrolyte abnormalities. Obtain ECG and electrolytes at baseline and periodically (e.g., every 1 to 2 months) during treatment as clinically indicated.

Contraindications

- None

Precautions/Warnings

- **Hemorrhage**: Fatal and serious cases of gastrointestinal and pulmonary hemorrhage. Monitor platelet counts and transfuse as needed.
- **Myelosuppression**: Panobinostat causes myelosuppression, including severe thrombocytopenia, neutropenia and anemia. Obtain a baseline CBC and monitor the CBC at least weekly during treatment. Monitor CBCs more frequently in patients over 65 years of age due to the increased frequency of myelosuppression in these patients.
- **Infections**: Monitor patients for signs and symptoms of infections during treatment; if a diagnosis of infection is made, institute appropriate anti-infective treatment promptly and consider interruption or discontinuation of panobinostat.
- **Hepatotoxicity**: Monitor hepatic enzymes and adjust dosage if abnormal liver function tests are observed during panobinostat therapy.
- **Embryo-Fetal Toxicity**: Can cause fetal harm. Advise women of the potential hazard to the fetus and to avoid pregnancy while taking panobinostat. Advise sexually-active females of reproductive potential to use effective contraception while taking panobinostat and for at least 3 months after the last dose. Advise sexually active men to use condoms while on treatment and for 6 months after their last dose.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

C9399	Unclassified drugs or biologicals (Hospital Outpatient Use ONLY)
J8999	Prescription drug, oral, chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

C90.00	Multiple myeloma not having achieved remission
C90.02	Multiple myeloma in relapse
C90.10	Plasma cell leukemia not having achieved remission
C90.12	Plasma cell leukemia in relapse
C90.20	Extramedullary plasmacytoma not having achieved remission
C90.22	Extramedullary plasmacytoma in relapse
C90.30	Solitary plasmacytoma not having achieved remission
C90.32	Solitary plasmacytoma in relapse

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Common Terminology Criteria for Adverse Events (CTCAE) - standardized definitions for adverse events published by the National Cancer Institute to describe the severity of organ toxicity for patients receiving cancer therapy. Toxicity is graded as mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4), with specific parameters according to the organ system involved.

Heavy chain – the larger component of an immunoglobulin. There are five types: IgG, IgA, IgM, IgD, and IgE.

Immunoglobulins (a.k.a., antibodies) – proteins made by normal plasma cells that have an important role in fighting infection as part of the humoral immune response. Antibodies are composed of two heavy chains and two light chains that form a larger complex. Each plasma cell produces only one type of heavy chain and one type of light chain.

Light chain – the smaller component of an immunoglobulin. There are two types: kappa and lambda.

Minimal response (MR) (according to the Revised Uniform Response Criteria by the International Myeloma Working Group) – **ALL** of the following:

- ≥25% but ≤49% reduction of serum M-protein
- Reduction in 24-hour urine M-protein by 50% to 89%
- In addition, if present at baseline, 25% to 49% reduction in size of soft tissue plasmacytomas is also required
- No increase in size or number of lytic bone lesions (development of compression fractures dose not exclude response).

Myeloma Protein (M-Protein) – a nonfunctional immunoglobulin protein or protein fragment produced by malignant plasma cells (or myeloma cells). Since myeloma cells are monoclonal, the M-proteins for a given patient are structurally identical. Both portions of an immunoglobulin (the heavy chain and light chain) can be found in the serum, while only light chains can be found in the urine.

Plasma cell - a fully differentiated B lymphocyte (a type of white blood cell) that is specialized for immunoglobulin production and is found primarily in bone marrow.

Primary refractory MM - patients who never achieve at least a MR to initial induction therapy and progress while on therapy

Progressive MM - at least a 25% increase from nadir in the serum M-protein (absolute increase must be ≥0.5 g/dL) or urine M-protein (absolute increase must be ≥200mg/24 hours), or in the difference between involved and uninvolved serum-free light-chain (FLC) levels (with an abnormal FLC ratio and FLC difference >100 mg/L).

Relapsed and refractory MM - patients who never achieve at least a MR or who progress within 60 days of their last therapy

Serum free light chain assay (SFLCA) – a test that detects the amount of unbound or free light chains (i.e., not attached to a heavy chain) in the serum. Normal values - kappa: 3.3 to 19.4 mg/L, lambda: 5.71 to 26.3 mg/L, kappa/lambda ratio: 0.26–1.65 (0.37–3.1 if renal impairment).

Serum Protein Electrophoresis (SPEP) – a test that detects and quantifies the amount of M-protein in the serum. An serum M-protein of greater than 30 g/L is consistent with a diagnosis of MM.

Smoldering (Asymptomatic) myeloma: defined as M-protein in serum of 30 g/dL or more AND/OR bone marrow clonal plasma cells of 10% or more and no related organ or tissue impairment (no end organ damage, including bone lesions) or symptoms.

RELATED GUIDELINES:

Allogeneic Bone Marrow and Stem Cell Transplantation, 02-38240-01

Bortezomib (Velcade) IV, 09-J0000-92

Carfilzomib (Kyprolis) IV, 09-J1000-81

Daratumumab (Darzalex) IV, 09-J2000-49

Doxorubicin HCl Liposome (Doxil) IV, 09-J0000-91

Elotuzumab (Empliciti) Injection, 09-J2000

Ixazomib (Ninlaro) Capsule, 09-J2000-51

Lenalidomide (Revlimid), 09-J0000-80

Pomalidomide (Pomalyst) Capsule, 09-J1000-95

Thalidomide (Thalomid) Capsules, 09-J1000-56

OTHER:

None

REFERENCES:

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12. San-Miguel JF, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014;15:1195-206.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 06/12/19

GUIDELINE UPDATE INFORMATION:

06/15/15	New Medical Coverage Guideline.
11/01/15	Revision: ICD-9 Codes deleted.
06/15/16	Review and revision to guideline consisting of updating the description section, position statement, definitions, billing/coding, related guidelines, and references.
02/16/17	Revision: Update to Position Statement.
07/15/17	Review and revision to guideline consisting of updating the description section, position statement, precautions, and references.
07/15/18	Review and revision to guidelines consisting of updating the description section, position statement, and references.
07/15/18	Review and revision to guidelines consisting of updating the description section, position statement, and references.